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A naturalistic study exploring the association between sleep and cognition in children with tic disorders

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VOLUME I

SYSTEMATIC LITERATURE REVIEW AND EMPIRICAL RESEARCH PROJECT

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Overview

Systematic Literature Review:

Empirical Research Project:

Systematic Literature Review

Sleep difficulties in children with Tourette syndrome and chronic tic disorders: A systematic review of characteristics and associated factors

Supervised by:

Professor Tony Charman

Dr Sally Robinson

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and

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List of tables and figures

1. Abstract

Background: Sleep disturbances are common in children and young people with Tourette syndrome and chronic tic disorders (TS/CTD), although at present it is unclear whether any particular sleep problems could be considered typical of these conditions. It is also not known whether any identified patient characteristics, neurodevelopmental or psychiatric factors are associated with their presence in this group.

Objectives: This review aimed to systematically explore types and frequency of sleep problems in children with TS/CTD. It aimed to examine the heterogeneity of previous studies in terms of sample characteristics and assessment methods and consider methodological quality of included studies.

Methods: The Psycinfo, Ovid Medline, Embase and Web of Science databases were searched using a range of terms relating to tics, sleep and co-existing psychopathology. Studies were considered if they met a pre-determined set of criteria, including a sample of children with TS/CTD (n>5) for whom sleep disturbance was measured. 14 studies met criteria for inclusion in the review.

Results: Overall, this review supported the high prevalence of sleep difficulties in children with TS/CTD, although rates varied widely from 17% to 80.4% (Interquartile Range (IQR) =21%-48%). A number of studies reported on other factors affecting sleep in this patient group including comorbidity, medication use and sample-related factors, such as age and gender. Studies varied in terms of methodology, sample and quality.

Conclusions: The high rates of sleep problems in children with TS/CTD identified in this review, which was based on a small yet heterogeneous sample of papers, highlights the need for continued research in this area. The potential moderating factors and associated difficulties discussed here should be considered further to enhance understanding of the aetiology and management of sleep difficulties in this group.

2. Introduction

It is widely recognised that children and young people with Tourette syndrome (TS) and chronic tic disorders (CTD) frequently experience difficulties sleeping (Kirov, Becker & Rothenberger, 2014). However, as yet the nature and specificity of these problems have not been identified, with a wide range of disturbances being reported in previous literature (e.g. Storch, Milsom, Lack, Pence, Geffken, Jacob et al., 2009). It is unclear whether this reflects true heterogeneity of the difficulties or methodological variation between studies. The present review aims to provide a comprehensive overview of existing research about sleep in TS/CTD with the hope of clarifying the current state of knowledge and offering directions for future study.

2.1 Sleep

2.1.1 Overview

Sleep is an active physiological state during which information acquired over waking hours is processed (Astill, Van der Heijden, Van Ijzendoorn & Van Someren, 2012). It is characterised by changes to cardiovascular and neuronal functioning, posture, mobility, level of alertness, eyelid movement, respiration and body temperature (Gregory & Sadeh, 2016). Sleep is understood to be comprised of different stages beginning with non-rapid eye movement (N-REM), which incorporates three progressively deeper states from one and two to the third stage, known as slow wave sleep (SWS). The final, quite distinct, stage is rapid eye movement (REM) sleep. During a sleep period these stages occur in repeating cycles (Ashworth, Hill, Karmiloff-Smith & Dimitriou, 2014).

During typical development sleep duration, patterns, architecture and stage distribution change in a maturational process which depends on age and central nervous system (CNS) development (MacLean, Fitzgerald & Waters, 2015). Thus, sleep difficulties might be expected in disorders involving altered CNS function including neurodevelopmental and neuropsychiatric conditions. However, sleep is a complex and vulnerable state which can be affected by a wide range of physiological, psychological and environmental factors (Gregory & Sadeh, 2016). Sleep problems can present as clinically significant conditions (e.g. hypersomnolence or circadian rhythm disorders; American Psychiatric Association, 2013) or as sub-clinical disturbances. As mentioned, sleep disturbance often occurs alongside, or is symptomatic of, conditions such as depression (Devnani & Hedge, 2015) and attention deficit hyperactivity disorder (ADHD; Astill et al., 2012). These disorders and sleep influence each other bidirectionally and can risk developing into a 'vicious cycle' (i.e. poor sleep worsens depression symptoms, which impacts sleep; Kahn, Sheppes & Sadeh, 2013).

Sleep difficulties affect daytime functioning, being predictive of emotional and behavioural difficulties as well as cognitive and academic performance (Wang, Isensee, Becker, Wong, Eastwood, Huang et al., 2016; Axelsson, Williams & Horst, 2016; Blechner & Williamson, 2016). Identifying and managing sleep difficulties promptly is therefore crucial to minimise their impact on psychosocial functioning. When sleep problems co-occur with neurodevelopmental or psychiatric disorders their presentation is often thought to be disorder-specific, possibly reflecting varying aetiological factors (Blackmer & Feinstein, 2016). Understanding different causes of sleep problems might facilitate the development of tailored interventions to improve sleep. Currently however, few clear disorder-specific sleep patterns are known and studies exploring these often reach conflicting conclusions. For instance, while ADHD is often thought to be characterised by frequent periodic limb movements in sleep (PLMS; Sadeh, Pergamin & Bar-Haim, 2006), this finding is not universal (Choi, Yoon, Kim, Chung & Yoo, 2010; Diaz-Roman, Hita-Yanez & Buela-Casal, 2016).

Sleep problems can be treated in various ways with adherence to good sleep hygiene principles (e.g. regular bedtime routines) being well-supported (Kaczor & Skalski, 2016). However, in children with additional difficulties these behavioural strategies may need to be adapted or augmented (e.g. including relaxation for anxiety; Ramtekkar & Ivanenko, 2015). Evidence for pharmacological treatments, regardless of the presence of other disorders, is mixed. For instance, while Melatonin reduces sleep latency it does not seem to impact sleep duration (Gringras, Gamble, Jones, Wiggs, Williamson, Sutcliffe et al., 2012). Furthermore, certain medications such as Selective Serotonin Reuptake Inhibitors (SSRIs), which are commonly prescribed to manage anxiety, can disrupt sleep so should be used cautiously in clinical groups predisposed to sleep problems (Kaczor & Skalski, 2016; Ramtekkar & Ivanenko, 2015; Mulraney, Giallo, Lycett, Mensah & Sciberras, 2016).

2.1.2 Sleep assessment

Sleep is therefore a complex phenomenon involving physiological and behavioural changes and can be assessed in various ways, broadly categorised into objective and subjective methods (Gregory & Sadeh, 2012). Polysomnography (PSG) is recognised as the 'gold standard' of objective sleep assessment and involves laboratory monitoring of neurophysiological and cardiorespiratory variables (Sadeh, 2015). PSG typically lasts one or two nights and generates extremely detailed information to enable clinical diagnosis of sleep disorders. However, it is costly and requires sleeping in a laboratory so is not especially representative of natural sleep patterns. A more naturalistic objective approach is actigraphy; this is conducted using a wristwatch-like device that continuously measures body movements to allow inferences to be made about sleep-wake patterns. It can be used in children's own homes and for periods of

several weeks, therefore is more reflective of typical sleep than PSG. However, it is less detailed and can be affected by movement artefacts. For this reason, it is proposed that outputs should be carefully monitored and assessed for accuracy which can be time-consuming (Meltzer, Wong, Biggs, Traylor, Kim, Bhattacharjee et al., 2016). Both approaches provide a range of sleep parameters including total sleep time, duration, number of stages, cycles and sleep efficiency (i.e. the amount of time in bed spent asleep). However, they do not generate information regarding children- or parent-perception of sleep difficulties. For this, subjective measures such as sleep diaries and questionnaires should be used.

Sleep diaries typically include information about sleep schedule and behaviours that might affect sleep. However they are not standardised and rarely generate information about other aspects of functioning or wellbeing. Questionnaires are a time- and cost-effective standardised way to gather this information. A range of validated sleep assessment questionnaires exist, however many rely solely on parent-report. This can be problematic as parent- and child-reports of sleep variables are often discrepant (Ji & Liu, 2016; Storch, Murphy, Lack, Geffken, Jacob & Goodman, 2008). Ideally, multiple informants should be consulted whenever possible. Overall, subjective measures are flawed due the complexity of sleep, as this makes it difficult to measure by pre-set criteria (Ji & Liu, 2016). Questionnaires can also be affected by factors including expectations, psychological influences and responder bias (Danker-Hopfe, 2011). Objective and subjective outcomes tend to correlate weakly (Tremaine, Dorrian & Blunden, 2010; Choi et al., 2010), suggesting they measure different aspects of sleep. Using multiple assessment methods is therefore recommended to produce a comprehensive overview of sleep difficulties and their functional impact (Gregory & Sadeh, 2016).

2.2 Tourette syndrome and chronic tic disorders

Gilles de la Tourette syndrome (TS) is a complex neuropsychiatric condition that was first described by Neurologist Georges Gilles de la Tourette in an 1885 paper on nine patients with a ‘malady of tics’, including involuntary movements and sounds (Lajonchere, Nortz & Finger, 1996). Current diagnostic manuals (DSM-V; American Psychiatric Association, 2013) characterise TS by the presence of two or more motor tics and at least one phonic tic that have been present for at least one year, begin before 18 years of age, and are not caused by medications or health conditions. People with either motor or phonic tics who meet these criteria can be diagnosed with chronic tic disorders (CTD; American Psychiatric Association, 2013). Overall prevalence estimates for TS in childhood are around 0.77% (Knight, Steeves, Day, Lowerison, Jette & Pringesheim, 2012) although TS may present more mildly in the community than in clinics, thus potentially making this an underestimation (Robertson, 2000).

TS/CTDs are approximately four times more common in males than females (Freeman, Fast, Burd, Kerbeshian, Robertson, & Sandor, 2000).

Tics are brief sudden movements or sounds sometimes preceded by a premonitory sensation ('urge'). They are suggestible, suppressible and typically occur with variable frequency ('waxing and waning'; Kumar, Trescher & Byler, 2016). Tics usually first appear during childhood with a mean emergence around six years of age before peaking in severity around 10-12 years of age. They tend to improve in adolescence, often disappearing by adulthood (Bloch & Leckman, 2009; Freeman et al., 2000). Tics can be simple or complex. 'Simple' tics involve single muscles or sounds (e.g. eye-blinking, coughing, throat clearing), while 'complex' tics include movement of multiple muscles or body parts, speaking phrases or strings of sounds. Complex tics can also include copying other people's movements ('echopraxia'), copying of speech ('echolalia') or making obscene gestures or comments ('copraphenomena'). Tics can negatively impact on quality of life with physical pain following certain motor tics, and phonic tics or copraphenomena often causing embarrassment and distress (Eapen, Cavanna & Robertson, 2016).

In line with its complex nature, the aetiology of TS is thought to be multifactorial including genetic vulnerability (Forde, Kanaan, Widomska, Padmanabhuni, Nespoli, Alexander et al., 2016), neuroinflammatory and autoimmune processes (Spinello, Laviola & Macri, 2016), pre- and peri-natal insults (Ludolph, Roessner, Munchau & Muller-Vahl, 2012) and androgenous influences (Smith & Dahodwala, 2014). However, at present the mechanisms through which different factors may combine to cause TS are unclear. Furthermore, despite being recognised as a neurological disorder, the neuroanatomical basis of TS is not well understood with mixed findings regarding the brain regions involved in its development and maintenance. This may be due to methodological differences across studies as well as the phenotypic complexity of TS (Forde, Zwiers, Naaijen, Akkermans, Openneer, Visscher et al., 2017). The most consistent evidence associates TS with changes in dopamine-mediated neural regions involved in inhibition, habit formation and reward, which encompass a cortico-striatal-thalamo-cortical network (Mink, 2001). Enhanced connectivity between the striatum and thalamus and motor, frontal, parietal and temporal regions is one factor thought to underpin tic genesis (Greene, Schlagger & Black, 2015). Despite evidence for dopaminergic changes in TS, patients also show altered transmission of serotonin, glutamate, and gamma-aminobutyric acid (GABA; Paschou, Fernandez, Sharp, Heiman & Hoekstra, 2013), thus implicating a wider neural network than only dopaminergic regions in its pathophysiology (Mink, 2001). Despite their clear neurobiological basis, tics are also exacerbated by environmental and contextual factors (e.g. stress; Gunduz & Okun, 2016). Stressful events are thought to exacerbate tics both

physiologically through activation of the hypothalamic-pituitary-adrenal (HPA) axis, and behaviourally via impaired capacity for suppression (Godar & Bortolato, 2016; Tagwerker & Walitza, 2016). Overall therefore, the aetiology of TS is poorly understood with different neural circuits and environmental factors likely to be implicated in different symptoms which may change during development.

In line with the varied aetiology and neurobiology of TS, and to facilitate thinking around its heterogeneous presentation, attempts have been made to subtype TS. A common distinction differentiates between 'pure TS' (tics only), 'TS plus' (TS with echo- and copraphenomena) and 'full blown TS' ('TS plus' with comorbid neurodevelopmental and/or psychiatric difficulties; Robertson & Baron-Cohen, 1998). Within 'full blown TS' comorbidities are wide-ranging (Kumar et al., 2016) and include neurodevelopmental (e.g. autism spectrum disorder; ASD), anxiety (e.g. obsessive compulsive disorder; OCD), mood (e.g. depression) and behavioural disorders (e.g. ADHD). A previous systematic review found that the most common comorbidities, presenting in 40-80% of patients, were behavioural disorders (e.g. ADHD), followed by OCD which occurs in 11-80% of patients (Ferreira, Pio-Abreu & Januario, 2014).

Comorbidity is a key determinant of health-related quality of life for people with TS/CTD who may require extra support to understand and manage these additional conditions or difficulties (e.g. sleep disturbance; Cavanna, David, Bandera, Termine, Balottin, Schrag et al., 2013). In line with this, researchers have begun to explore interactions between TS/CTD and other disorders. Much of this research has considered neurobiological profiles (Sambrani, Jakubovski & Müller-Vahl, 2016), with initial genetic and neuroimaging studies suggesting more similarities between TS/CTD and OCD than TS/CTD and ADHD (Greene, Williams, Koller, Schlagger & Black, 2016). This might suggest that OCD and TS/CTD could be causally linked, while ADHD is a distinct but common comorbidity. This work is preliminary but may impact on management and intervention of each disorder within the context of tics, as well as co-occurring problems such as poor sleep.

2.3 Sleep in TS/CTD

Sleep difficulties have been identified in TS/CTD patients (Kirov et al, 2014), however, in line with research into other disorders, their frequency, nature and aetiology is unclear (Kirov et al., 2014). A fairly consistent finding is that TS/CTD patients exhibit a high level of movement during sleep (Cohrs, Rasch, Altmeyer, Kinkelbur, Kostanecka, Rothenberger et al., 2001). It is unclear whether this represents a disorder-specific sleep difficulty, or whether movements are caused by transdiagnostic influences such as medication use (Arana-Lechuga, Sanchez-Escandon, Santiago-Trevino, Castillo-Montoya, Teran-Perez & Velaquez-Moctezuma,

2008). Furthermore, in samples of children with TS/CTD and comorbid ADHD, sleep difficulties can almost entirely be accounted for by ADHD symptoms, suggesting they may reflect comorbid factors rather than being characteristic of TS/CTD per se (Freeman, 2007).

Disorder-specific hypotheses draw on observations of shared neurobiological changes between sleep disturbance and TS/CTD. For instance, certain genes implicated in the aetiology of TS/CTD also cause sleep-related movement problems (e.g. PLMS; Muller, Voderholzer, Kurtz & Straube, 1994). Neurochemically, as previously discussed, dopamine is thought to be implicated in TS/CTD development (Mink, 2001). Sleep disturbances can be treated in TS patients with pharmacological agents that block dopaminergic systems, suggesting a common dopaminergic basis for sleep- and movement-disorders (Arana-Lechuga et al., 2008). Furthermore, reduced intracortical inhibition (i.e. increased arousal) of motor pathways is a common factor in TS/CTD and sleep disturbance (Happe & Trenkwalder, 2002). Sleep difficulties in TS/CTD appear to differ based on individual factors such as age and gender. They appear to be less prevalent in adults than children although it is unclear whether this is linked to changes in tic-related pathophysiology (i.e. hormones, neurological structure or function), improved management of other factors (i.e. receiving treatment for anxiety) or behavioural changes (i.e. better sleep hygiene; Freeman, 2007). Sleep problems may also be more common in females than males with TS, which could support a role for hormonal processes in development of sleep disturbance (Sambrani et al., 2016) or reflect gender-specific patterns of comorbidity or tic severity (Lichter & Finnegan, 2015).

Alternatively, sleep disturbance in TS/CTD may be caused by medication-use. Pharmacotherapy is the most common treatment for TS/CTD and the most frequently prescribed medications (Clonidine, Aripiprazole and Risperidone; Rickards, Cavanna & Worrall, 2012) all affect sleep (Hollis, Pennant, Cuenca, Glazebrook, Kendall, Whittington et al., 2016). Furthermore, concerns about sleep disturbance are commonly cited by parents and young people as a reason for refusing psychopharmacological treatment (Cuenca, Glazebrook, Kendall, Hedderly, Heyman, Jackson et al., 2015).

It is therefore unclear whether sleep difficulties are linked directly with TS/CTD pathology (at a hormonal, genetic or neuroanatomical level), whether they are caused by comorbid neurodevelopmental difficulties, pharmacological treatments or result from a combination of these factors (Kirov et al., 2014). It would be helpful to comprehensively consider the characteristics of sleep in varied samples of children with TS/CTD to see if clear disorder-specific patterns emerge.

2.4 Review aims

Evidence suggests that people with TS/CTD experience sleep difficulties. However, as previously mentioned, to the author's knowledge, no formal systematic review has yet been undertaken to fully summarise this area. The current review aims to provide this overview and has two main aims:

1. To explore the types and frequency of sleep difficulties in children with TS/CTD.
2. To consider additional factors that may contribute to sleep difficulties in this group.

3. Method

3.1 Literature search

This review was based on a systematic search of papers published before May 2016. The search was conducted in line with the guidelines of PRISMA (the Preferred Reporting Items for Systematic reviews and Meta-Analyses; Moher, Liberati, Tetzlaff & Altman, 2009) using two approaches:

Firstly, a computer search was conducted of the Psycinfo, Medline (ovid), Embase and Web of Science online databases. This search combined four separate components:

1. Tourette* Syndrome (OR) Tourette* (OR) tic* (OR) tic disorder (OR) chronic tics (OR) chronic tic disorder (OR) transient tic disorder
(AND)
2. Sleep (OR) sleep disorder (OR) sleep behavi?r (OR) sleep disturbance (OR) sleep difficult*
(AND)
3. Actigraph* (OR) polysomnograph* (OR) diary (OR) questionnaire (OR) self-report (OR) parent-report (OR) objective (OR) subjective
(AND)
4. Comorbid* (OR) Psycholog* (OR) Psychiat* (OR) disorder* (OR) mental health (OR) mood disorder* (OR) anx* (OR) dep* (OR) neurodevelopment*

Secondly, relevant journals were hand searched, along with reference lists of relevant papers and the bibliographies of frequently cited researchers.

Following this initial search, each stage of the review was conducted independently by two researchers (CH & ST) to reduce bias. Any disputes were raised with a third member of the review team if necessary. After the removal of duplicate papers (see Figure 1), 892 abstracts were screened for the following inclusion criteria: i) sample size ≥5 participants; ii) mean age of participants <18 years; iii) inclusion of participants with Tourette syndrome or chronic tics; iv) inclusion of a measure of sleep difficulty; v) empirically-based (i.e. not literature reviews) and peer reviewed (i.e. not dissertations or conference proceedings); vi) published in English.

Based on the inclusion criteria 77 studies were identified for more in-depth review. Of these, 63 papers were excluded with the following justifications: i) no clear measurement of sleep difficulty; ii) sample size <5; iii) mean age >18; iv) not being empirically-based or published in a peer-reviewed format; v) not being written in English. 8 papers could not be accessed by the researcher.

14 papers fulfilled criteria for inclusion in the final review.

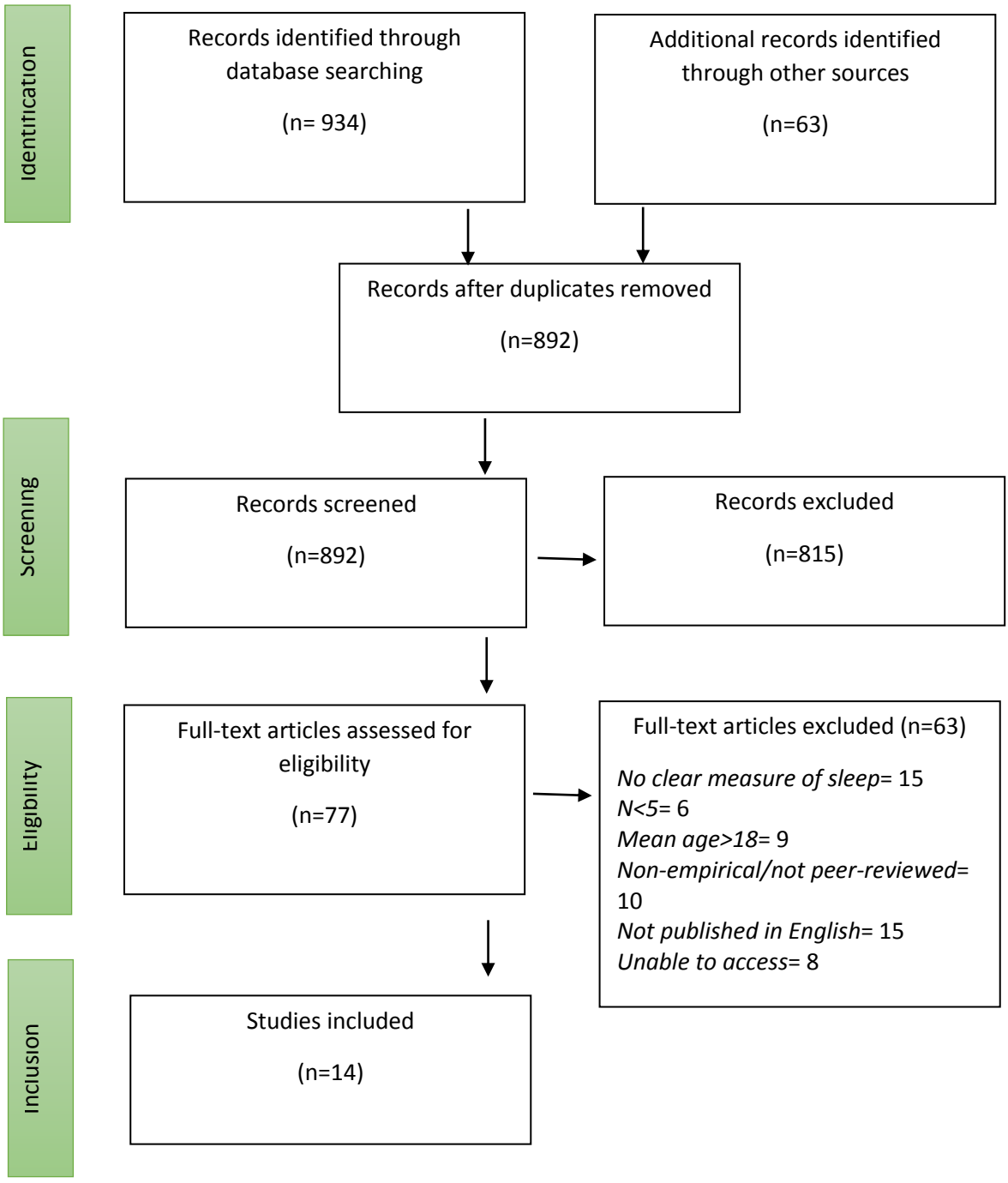

Figure 1: PRISMA flowchart

3.2 Data extraction

For eligible articles, data was extracted regarding the sample characteristics, study methods and results.

3.2.1 Sample characteristics

Information about sample characteristics was extracted from each paper relating to number of participants with TS/CTD, details of any comparison groups, recruitment site, age, gender and medication status of participants.

3.2.2 Methods and results

Data was extracted regarding methods used to measure sleep in each study, types of sleep difficulty assessed, main results and any additional relevant findings.

3.3 Quality assessment

Included articles were assessed for their methodological quality. As there is no agreed quality assessment tool for evaluating observational and prevalence studies (Mallen, Peat & Croft, 2006), a novel measure was developed drawing on criteria outlined by Loney, Chambers, Bennett, Roberts & Stratford (1998), Downs & Black (1998) and the Centre for Reviews and Dissemination guidance (2009). The scoring system is included in Appendix 1.

4. Results

Details of the 14 eligible studies are presented in Tables 1 and 2.

4.1 Participants

4.1.1 Recruitment source for TS/CTD participants

Included studies used a combination of clinical, convenience and community sampling methods. 12 studies (85%) recruited TS/CTD participants solely or partially from clinical services. Most of these were specialised university hospital clinics (Allen, Singer, Brown & Salam, 1992; Barabas & Matthews, 1984; Ghosh, Rajan, Das, Datta, Rthner & Erenberg, 2014; Kirov, Banaschewski, Uebel, Kinkelbur & Rothenberger, 2007a; Kirov, Kinkelbur, Banaschewski & Rothenberger, 2007b, Kostanecka-Endress, Banaschewski, Wüllner, Lichtblau, Cohrs, Rüther et al., 2003; Modafferi, Stornelli, Chiarotti, Cardona & Bruni, 2016; Mol Debes, Hjalgrim & Skov, 2008; Saccomani, Fabiana, Manuela & Giambattista, 2005; Stephens, Chung, Jovanovic, Guerra, Stephens, Sandor et al., 2007; Storch, Milsom, Lack, Pence, Geffken, Jacob et al., 2009 & Teive, Germiniani, Della Coletta & Werneck, 2001). Two studies (14%) used a charity to recruit some or all TS/CTD participants (Allen et al., 1992; Wand, Matazow, Shady, Furer & Staley, 1993). One study (7%) did not explicitly state how data was collected, but appeared to be a clinic-based project retrospectively exploring sleep using historical data (Hashimoto, Endo, Fukuda, Hiura, Kawano, Suzue et al., 1981).

4.1.2 Sample characteristics

4.1.2.1 Size

Sample sizes varied widely from nine (Hashimoto et al., 1981) to 314 participants (Mol Debes et al., 2008). The IQR for sample size was 42-237 participants.

4.1.2.2 Age

Age ranges were reported for 12 of the included studies (85%). All samples had a mean age under 18 years, but four studies included older participants up to 20 years (Mol Debes et al., 2008; Saccomani et al., 2005), 21 years (Ghosh et al., 2014) and 60 years (Tieve et al., 2001). Another study (Wand et al., 1993), included separate child and adult samples from which only child data was extracted for the present review.

4.1.2.3 Gender

All of the included studies commented on gender distribution of the sample. 13 studies included both male and female participants, with proportions ranging from 63.6% male and 36.4% female (Tieve et al., 2001) to 100% male (Allen et al., 1992).

4.1.2.4 Medication status

Medication status of participants was reported for seven of the included studies (50%; Allen et al., 1992; Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Mol Debes et al., 2008 & Stephens et al., 2007) Of these, three reported that participants took medications during the study or did not state a medication-free period (Allen et al., 1992; Modafferi et al., 2016; Mol Debes et al., 2008). One study (Allen et al., 1992), differentiated between participants taking different amounts of medication. The remaining four had a pre-study medication-free period from five days to six weeks (Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Stephens et al., 2007).

4.1.2.5 Tic disorder group characteristics

Of the 14 included studies, 13 (93%) had a 'pure TS' sample, or a TS sample without comorbidity described (Allen et al., 1992; Barabas & Matthews, 1984; Ghosh et al., 2014; Hashimoto et al., 1981; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Mol Debes et al., 2008; Saccomani et al., 2005; Stephens et al., 2013; Storch et al., 2009; Teive et al., 2001 & Wand et al., 1993). The remaining study (Kirov et al., 2007a), compared participants with comorbid TS+ADHD to healthy controls. Of the 13 studies with 'pure TS' samples, three distinguished between TS and CTD (Modafferi et al., 2016; Saccomani et al., 2005; Teive et al., 2001), one included TS-only and TS+patient- or family-migraine (Barabas & Matthews. 1984), and five had both TS-only and TS+ADHD groups (Allen et al., 1992; Ghosh et al., 2014; Kirov et al., 2007a; Kirov et al., 2007b & Stephens et al., 2013).

4.1.2.6 Control group

Of the included studies, eight had at least one non-TS/CTD group (57%; Allen et al., 1992; Hashimoto et al., 1981; Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Saccomani et al., 2005; Stephens et al., 2007). Of these, five had one comparison while the remaining three included two control groups (Allen et al., 1992; Kirov et al., 2007b & Stephens et al., 2007).

Table 1: Study characteristics

Paper reference	N with TS	Number and details of comparison groups	Sample type/recruitment site	Age range (mean/SD-if avail)	% males/females	Medication status of Pps	Quality rating (/14)
Allen et al (1992)	TS only=57 TS+ADHD=89	ADHD-only=21 HC=146	TS: Specialist clinic & TS associations HC: Local schools	Overall range =7-14 HC= (10.8/1.8) TS-only= (II.6/2.0) TS+ADHD= (10.9/1.9) ADHD-only=(10.4/2.0)	100% M	1 medication: 58% of TS pps (27/57 TS only; 57/89 TS+ADHD) 2/>: 4/27 TS-only; 12/57 TS+ADHD	10
Barabas & Matthews (1984)	TS-only=27 (group 2) TS+ patient migraine=18 (group 1a) TS+primary relative with migraine=20 (group 1b)	N/A	Specialist clinic	Group 2=12.1 Group 1a=11.6 Group 1b=9.7	Group 2=77.78% M; 22.22% F Group 1a=77.78% M; 22.22% F Group 1b=95% M; 5% F	N/R	4
Ghosh et al (2014)	TS-only=48 TS+ADHD=75	N/A	Specialist clinic	Overall range=6-21 (13.6/3.8) TS-only=14.4 (3.6) TS+ADHD=13.2 (3.9)	TS-only=80% M; 20% F TS+ADHD=66.7% M; 33.3% F	N/R	3
Hashimoto et al (1981)	TS=9	HC= number unclear	N/R	4-12	TS group=77.78% M; 22.22% F HC=N/R	N/R	7

Kirov et al (2007a)	TS+ADHD=19	HC=19	TS+ADHD: Specialist clinic HC: friends and relatives of staff	TS+ADHD=8.2-16.2 (11.07/2.26) HC-8-15 (11.09/2.23)	TS+ADHD=94.74 % M; 5.26% F HC= 89.47% M; 10.53% F	63.16% of TS+ADHD pps took medication; all had 7 medication-free days prior to study.	11
Kirov et al (2007b)	TS-only=18 TS+ADHD=18	ADHD-only=18 HC=18	TS+ADHD: Specialist clinic HC: friends and relatives of staff	TS-only=8-15.7 (11.74/2.31) TS+ADHD=8.2-16.4 (11.10/2.33) ADHD-only=8.2-14.9 (10.94/1.99) HC=8-15.6 (11.58/2.25)	TS-only= 88.89% M; 11.11% F TS+ADHD=94.44 % M; 5.56 % F ADHD-only=94.44% M; 5.56 % F HC=88.89% M; 11.11% F	72.22% of TS+ADHD & ADHD-only and 61.11% of TS-only children were medicated; all had 5-14 medication-free days prior to study.	11
Kostanecka-Endress et al (2003)	TS=17	HC=16	TS: Specialist clinic HC: convenience method	TS=7.11-15.5 (11.10) HC=11.78	TS=70.58% M; 29.42 % F HC=75% M; 25% F	58.83% of pps had been medicated; all had at least 14 medication-free days prior to study.	11
Modafferi et al (2016)	TS=36 78%=TS 22%=Chronic motor/phonic tic disorder	HC=266	TS: Specialist clinic HC: schools	TS=8-16.3 (11.7) HC mean=11.5 years	TS=83.30% M; 16.70% F HC=71.80% M; 28.20% F	30.56% of TS pps were taking medication for tic management at the time of the study	8
Mol Debes et al (2008)	TS=314	N/A	Specialist clinic	5.3-20 (12.4)	81.9% M; 18.1% F	7.7%=methylphenidate 1.6% 'treated medically for OCD'	7
Saccomani et al (2005)	TS=48 CTD=48	HC=30	TS=Specialist clinic HC: convenience method	TS=4.6-17.8 (11.2) CTD=5.10-20 (12.1) HC=6.4-13.10 (10.8)	TS=75% M; 25% F CTD=68.75% M; 31.25% F	N/R	6

					HC=66.67% M; 33.33% F		
Stephens et al (2013)	TS=20 TS+ADHD=21	ADHD=33 HC=16	TS=Specialist clinic ADHD & HC= community paediatricians, general hospital, family doctors and community posters	Total sample=6-16 (10.8)	Total sample=83.3% M; 16.7% F	All pps were at least 6 weeks free of medication & 72.4%=medication naïve	11
Storch et al (2009)	TS/CTD=56	N/A	Specialist clinic	7-17 (11.46 +- 2.63)	71.42% M; 28.58% F	N/R	7
Teive et al (2001)	TS=33 Chronic tics=10 Transitory tics=1	N/A	Specialist clinic	3-60 (13.5)	63.6% M; 36.4% F	N/R	4
Wand et al (1993)	TS=446 overall; 245<18 years	N/A	Charitable organisation	Of group <18, mean=11.9 (2.9)	Of group <18 84.8% M; 15.2% F	N/R	6

N/A=not applicable; N/R=not reported; HC=healthy controls TS=Tourette syndrome; CTD=chronic tic disorder ADHD=attention deficit hyperactivity disorder

4.2 Methods

Table 2 includes information about the methods used to assess sleep. For one study (Barabas & Matthews, 1984), methodology was not discussed in sufficient detail to be included here.

4.2.1 Subjective methods

Subjective sleep measures were used in nine of the 14 studies (64%). Methods included parent report or interview (n=1; Saccomani et al., 2005), review of clinic records (n=1; Teive et al., 2001) and questionnaires (n=7). Of the questionnaire studies, three developed novel measures (Ghosh et al., 2014; Modafferi et al., 2016; Wand et al., 1993), while four used or adapted validated scales (Allen et al., 1992; Kostanecka-Endress et al., 2003; Mol Debes et al., 2008; Storch et al., 2009). These included the Sleep Behaviour Questionnaire (Simonds & Parraga, 1982); the sleep scale of the Children's Behaviour Checklist (CBCL; Achenbach & Rescorla, 2011), and items from the Multidimensional Anxiety Scale for Children (MASC; March, 1998). Four of the seven questionnaire studies (58%) used only parent-report measures (Allen et al., 1992; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Mol Debes et al., 2008), while the remaining three (42%) also asked children about their sleep (Ghosh et al., 2014; Storch et al., 2009; Wand et al., 1993). No studies used child-report only.

4.2.1.2 Types of sleep difficulty assessed by subjective means

Most studies considered a wide range of general sleep behaviours and difficulties[1] (Allen et al., 1992; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Wand et al., 1993; Mol Debes et al., 2008; Storch et al., 2009), whilst two had more specific parameters (e.g. Barabas & Matthews, 1984; Wand et al., 1993). Three studies reported prevalence of DSM-coded sleep disorders (e.g. insomnia; Ghosh et al., 2014; Saccomani et al., 2005; Tieve et al., 2001).

4.2.2 Objective methods

Sleep was assessed objectively in five of the included studies (36%). One study (Hashimoto et al., 1981) included one night polygram, while the remainders used two consecutive nights of PSG (Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Stephens et al., 2007). One study used both objective and subjective methods (Kostanecka-Endress et al., 2003).

[1] Further information about the range of sleep difficulties is provided in Table 2

4.2.2.2 Types of sleep difficulty assessed by objective means

All PSG studies considered a wide range of physiological sleep variables including analysis of sleep stages and cycles. These studies also reported on sleep efficiency, sleep onset latency, degree of movement and microarousals during sleep. Hashimoto et al (1982) specifically explored different types of movement, including body movements and twitches throughout the night.

4.3 Results

Table 2 outlines the main sleep-related findings for each study.

4.3.1 Overall findings regarding sleep difficulties in TS/CTD

All 14 included studies found that participants with TS/CTD had more disturbed sleep than healthy controls. Estimates of sleep difficulty in TS/CTD-only participants ranged from 17-80.4% (IQR=21-48), while estimates for controls were 0%-10% (Allen et al., 1992; Mol Debes et al., 2008; Saccomani et al., 2005; Storch et al., 2009). Rates of DSM-coded sleep disorders in TS/CTD ranged from 9%-65% (Ghosh et al., 2014; Tieve et al., 2001). One study compared rates of sleep disorders for a TS-only group and healthy controls, finding 0% in controls (Saccomani et al., 2005). In one study sleep difficulties were reported to significantly impact on daily functioning (Ghosh et al., 2014).

Studies directly comparing clinical samples found that sleep difficulties were most common in ADHD-only, followed by TS+ADHD, then TS-only (Allen et al., 1992; Ghosh et al., 2014). Furthermore, participants with ADHD, regardless of TS-status (i.e. TS+ADHD or ADHD-only) showed a particular sleep pattern featuring more time in bed, a longer total sleep time, higher percentage of REM sleep, more sleep cycles, shorter latency of stages one, two and REM sleep and more leg movements during sleep compared to those without ADHD (i.e. TS-only or healthy controls; Stephens et al., 2013; Kirov et al., 2007b).

4.3.1.1 Sleep initiation and onset in TS/CTD

Findings regarding sleep initiation and onset were inconsistent, with studies directly measuring initiation finding no significant difference between participants with comorbid TS+ADHD and healthy controls, or between TS-only and TS+ADHD (Kirov et al., 2007a; Ghosh et al., 2014). However, considering pre-sleep factors more generally, a majority of TS parents reported their children had 'problems getting to sleep' (Wand et al., 1993), anxiety and fear

around sleep, reluctance to go to sleep and need for transitional objects or sleep aids (Modafferi et al., 2016).

4.3.1.2 Sleep maintenance and duration

Only one study directly commented on sleep maintenance, finding it to be significantly more problematic in participants with TS+ADHD compared to TS-only (Ghosh et al., 2014). However, compared to other groups, parents of TS-only participants reported a significant degree of short restless sleep (Modafferi et al., 2016), wakefulness after sleep onset (Kostanecka-Endress et al., 2003), and difficulty staying asleep (Wand et al., 1993). Additionally, participants with TS/CTD ± ADHD spent longer in bed and had a longer sleep period than controls (Kirov et al., 2007a).

4.3.1.3 Sleep efficiency

Two studies directly commented on sleep efficiency, finding it to be reduced in TS/CTD compared to healthy controls and ADHD-only participants (Kirov et al., 2007b; Kostanecka-Endress et al., 2003

Two studies found that TS participants reported more tiredness on waking and daytime sleepiness (Modafferi et al., 2016; Storch et al., 2009), which could also suggest less efficient overnight sleep. Additionally, three studies reported significant levels of behaviours that could be considered 'sleep-interfering', including nightmares (Modafferi et al., 2016; Storch et al., 2009), bruxism, snoring (Modafferi et al., 2016), and sleepwalking (Wand et al., 1993).

4.3.1.4 Sleep stage analysis

Studies reporting on sleep stages were inconsistent. Children with TS+ADHD showed a significantly higher percentage of REM sleep with a shorter REM latency and increased latencies of stages one to three than healthy controls (Kirov et al., 2007a; 2007b). Contrastingly, Kostanecka-Endress et al (2003), found no significant difference in REM sleep duration or cycle latencies between TS and healthy controls, although TS participants had less stage two sleep.

4.3.1.5 Movements during sleep

Hashimoto et al (1981) found a different movement pattern in TS participants compared to healthy controls. This included more body movements and twitch movements during REM sleep. TS participants also reported significantly more hypnic jerks during sleep

than controls (Modafferi et al., 2016), and had more motor-related and microarousals during sleep (Kirov et al., 2007a; 2007b).

4.3.1.6 PLMS/SDB

Four studies reported on prevalence of PLMS and Sleep-Disordered Breathing (SDB). Two reported no SDB (Kirov et al., 2007a; Kostanecka-Endress et al., 2003), and infrequent PLMS (Kostanecka-Endress et al., 2003). The remaining two studies observed PLMS and SDB only in participants with comorbid TS+ADHD (Kirov et al., 2007b; Stephens et al., 2007).

4.3.2 Additional findings

Additional findings considered relevant to the current analysis were reported in 10 of the 14 included studies (71%). These included links between sleep and participant characteristics, tic severity, medications, and comorbid internalising and externalising difficulties.

4.3.2.1 Participant characteristics

Two studies (14%) considered the impact of participant characteristics on sleep (Stephens et al., 2007; Storch et al., 2009), these included age, pubertal status and gender. It was found that younger children had more total sleep problems and that pubertal stage was linked with total sleep time and percentage of SWS, although the direction of this effect was unclear (Storch et al., 2009; Stephens et al., 2007). Storch et al (2009) found that females had more sleep difficulties than males.

4.3.2.2 Tic severity

Four of the included studies (29%) correlated tic severity and sleep (Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Storch et al., 2009). Two studies found that increased tic severity linked to reduced sleep efficiency, increased overall latency, increased microarousals during REM sleep, hypnagogic hallucinations, sleep talking and parasomnias (Kirov et al., 2007b; Modafferi et al., 2016). Two studies (Kostanecka-Endress et al., 2003; Storch et al., 2009), observed no association between overall severity and sleep parameters, although motor tic severity was negatively associated with total sleep-related problems (Storch et al., 2009).

4.3.2.3 Medications

Four studies explored relationships between medication-use and sleep (Allen et al., 1992; Ghosh et al., 2014; Kostanecka-Endress et al., 2003; Modafferi et al., 2016). Two found no difference in the physiological or reported sleep parameters of medication-naïve or

previously medicated and currently medicated or unmedicated participants (Kostanecka-Endress et al., 2003; Modafferi et al., 2016). In those finding an association, medication was the primary cause of insomnia in 33% and hypersomnia in 7% of one sample (Ghosh et al., 2014). Another study found antidepressants to be linked with unpleasant dreams and stimulants with enuresis (Allen et al., 1992).

4.3.2.4 Severity of ADHD symptoms in TS

Of the 14 studies, three (21%) considered relationships between severity and type of ADHD symptoms and sleep in TS patients (Kirov et al., 2007a; Kirov et al., 2007b; Stephens et al., 2007). In two studies ADHD symptom severity, as determined by Conner's score and degree of attentional problems, was associated with reduced REM sleep latency and increased duration of REM sleep (Kirov et al., 2007a; Kirov et al., 2007b). The latter study also found that hyperactivity was associated with an increased number of sleep cycles (Kirov et al., 2007b). Stephens et al (2007) supported the link between hyperactivity and sleep. They found that patients with TS+ADHD and high hyperactivity had more arousals during sleep than those with TS+ADHD with low hyperactivity and TS-only, although this was less than participants with ADHD-only at both levels of hyperactivity.

4.3.2.5 Mood and externalising difficulties

Five studies (36%) considered relationships between mood and sleep (Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Modafferi et al., 2016; Mol Debes et al., 2008; Storch et al., 2009). Overall, they tended to be related, though one study found no correlation when using CBCL score to measure mood (Kostanecka-Endress et al., 2003). In the remaining studies, quality of life, internalising symptoms and anxiety were all significantly related to number of sleep-related problems (Storch et al., 2009). Furthermore, CBCL score and tic severity when combined determined more short motor-related arousals in sleep (Kirov et al., 2007b). In another study scores of, or nearing, clinical significance for anxiety or depression were associated with abnormal movements pre-sleep (Modafferi et al., 2016). In one study, patients with TS and comorbid anxiety had the most sleep problems (Storch et al., 2009), while another found that those with multiple comorbidities were most at risk (Mol Debes et al., 2008). Another study linked obsessive-compulsive symptoms to problems falling asleep and reduced duration (Modafferi et al., 2016).

In terms of externalising behaviours, one study (7%) considered the relationship between sleep and the delinquency, conduct disorder, hyperactivity/immaturity and restlessness/disorganised behaviour scales of the CBCL (Achenbach & Rescorla, 2011; Stephens

et al., 2007). Delinquency was associated with number of movements during REM sleep, while the remaining scales were associated with total number of arousals and SWS arousals.

4.4 Methodological quality

Total methodological quality ratings are provided in Table 1. Full scores are presented in Appendix 2. Of a maximum of 14, scores ranged from three (Ghosh et al., 2014) to 11 (Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003 & Stephens et al., 2007). The average quality rating was 7.6, which is just over 50% of the maximum score. This suggests that the available research is of moderate quality, although highly heterogeneous. Items on which particularly low ratings were received included not adequately representing the TS population (i.e. single recruitment site or only specialist clinics; 12 studies), not justifying or commenting on sample size (12 studies), and not stating number to refuse participation (11 studies).

Table 2: Methods & results

Paper reference	Method(s) of sleep assessment (Informant/assessment duration)	Types of sleep difficulty assessed	Main sleep-related findings	Additional findings or associations
Allen et al (1992)	• Questionnaire (parents) Modified version of Sleep Behaviour Questionnaire (Simonds & Parraga, 1982)	Wide range of sleep behaviours	Sleep and behaviour complaints were significantly more common in TS and/or ADHD than controls. Overall 'poor sleep' was reported in: 26%=TS-only 41%=TS+ADHD 48%=ADHD-only 10%=HC	**Medications:** Antidepressants= associated with unpleasant dreams; Stimulants= associated with enuresis
Barabas & Matthews (1984)	• Not stated	Somnambulism Night terrors Enuresis	TS+Migraine=a significantly greater prevalence of disorders of arousal than TS-only. Highest prevalence=TS+patient migraine.	N/A
Ghosh et al (2014)	• Questionnaire (young person and at least one parent/guardian) Novel	Wide range of sleep problems assessed & prevalence of DSM-IV coded sleep disorders	Sleep maintenance problems and abnormal sleep behaviours were significantly more prevalent in TS+ADHD compared to TS-only. No significant differences in sleep Initiation. Both groups=high impact on daily functioning secondary to sleep disturbances,	**Medications:** <u>Hypersomnia secondary to medication</u> 3%=TS-only 4%=TS-+ADHD <u>insomnia secondary to medication</u> 0%=TS-only 33%=TS+ADHD

			but no significant difference between groups. <u>DSM-V sleep disorders</u> TS-only=65%; TS+ADHD=64% <u>Primary Insomnia</u> TS-only=32%; TS+ADHD=42%	
Hashimoto et al (1981)	• Sleep polygram (1 night)	<u>Twitch movements (TM)</u> Total sleep REM sleep non-REM sleep <u>Body movements (BM)</u> Total sleep REM sleep Non-REM sleep	6/9 TS Pps=EEG changes during sleep but no consistent effect across Pps. <u>TS vs HC</u> Significantly >BMs & different frequency of movements across sleep stages. Significantly >TM/min during REM sleep, but not during non-REM, or for total sleep time. <u>TS Pps within-group</u> Significantly >TM=REM vs non-REM.	N/A
Kirov et al (2007a)	• PSG (2 consecutive nights)	Wide range of physiological sleep variables	<u>TS+ADHD vs HC</u> >time in bed, sleep time, REM sleep %, microarousals in light & REM sleep & short motor-related arousals <REM sleep latency. -ve correlation=REM sleep latency & REM % <u>No significant differences</u> Sleep efficiency, onset, SWS latency, duration of wake, light sleep & SWS, % of movement & number of microarousals in SWS. No PLMS or SDB in either group.	**ADHD symptoms:** Conner's scores determined changes in REM sleep latency & REM duration.
Kirov et al (2007b)	• PSG (2 consecutive nights)	Wide range of physiological sleep variables	<u>TS-only & TS+ADHD vs ADHD-only & HC</u> <sleep efficiency >latency of sleep stages 1, 2 & 3,	**Tic severity:** Associated with <sleep efficiency, >sleep onset, >SWS latency & >microarousals in REM sleep.

			microarousals in REM sleep & short motor-related arousals. <u>ADHD-only & TS+ADHD vs TS-only & HC</u> >time in bed, sleep period, total sleep time, REM % & number of sleep cycles. <latency of sleep stage 1, 2 & REM sleep Only Pps with ADHD showed evidence of PLMS (11%) or SDB (5%).	**Tic severity + psychopathology (CBCL score):** Determined >short motor-related arousals. **Attentional problems:** Determined >REM duration & <sleep onset latency. **Hyperactivity**: Determined >sleep cycles.
Kostanecka-Endress et al (2003)	• Sleep items of CBCL (parents) • PSG (2 consecutive nights)	Wide range of physiological sleep variables	<u>TS Pps vs HC</u> > time in bed, sleep period, wakefulness after sleep onset & time awake during night <sleep efficiency & sleep stage 2 duration <u>No significant differences</u> Amount of REM, SWS or stage 1, total sleep time, numbers of sleep stage shifts, numbers of stages, duration or stage-latencies of each cycle. 1 pp=PLMS & 0 Pps=sleep apnea	**Medication use:** No difference in sleep parameters of medication-naïve and previously medicated Pps. **Tic severity:** No correlations with sleep parameters **Psychopathology:** No correlations with sleep parameters
Modafferi et al (2016)	• Questionnaire (parents) Novel	Range of sleep behaviours & difficulties during last 6 months	Significant differences on 15 of 45 questions. <u>TS Pps</u> >sleep duration <8 hrs, sleep difficulties, anxiety/fear around sleep, reluctance to go to bed, hypnic jerks, use of sleep aids (e.g. fluids, medications, light, tv), transitional objects, parasomnias, restless sleep, bruxism, snoring and daytime sleepiness.	**Tic severity: >**sleep latency, hypnagogic hallucinations, sleep talking & nightmares. **Medication use:** no difference, medicated vs unmedicated TS Pps but unmedicated TS Pps vs HC=>sleep breathing problems & hypnagogic hallucinations. **Psychopathology:** TS Pps with borderline/pathological SAFA-A or SAFA-D=>abnormal movements before sleep. TS Pps with borderline/pathological SAFA-O=>problems falling asleep &

				<sleep duration.
Mol Debes et al (2008)	• Questionnaire (parents) Sleep items of CBCL	'Sleep disturbances'(>6 on CBCL scale)	17% of Pps=score >6	**Psychopathology:** TS+ADHD+OCD=significantly > likely to have sleep disturbances than other groups (TS+ADHD, TS/OCD or TS-only).
Saccomani et al (2005)	• Parent report/interview	Degree of 'sleep problems', based on DSM-IV-TR criteria.	Present in: TS group=27.1% CTD group=16.7% HC=0%	N/A
Stephens et al (2013)	• PSG (2 consecutive nights)	Wide range of physiological sleep variables	<u>TS+ADHD vs other groups</u> >PLMS <u>TS+ADHD & ADHD-only vs other groups</u> >leg movements in sleep <u>ADHD-only vs other groups</u> >movements during REM sleep, total arousals from sleep & arousals from SWS	**Hyperactivity:** ADHD-only (low- and high-hyperactivity)=>total arousals than TS-only, TS+ADHD low-hyperactivity & controls. TS+ADHD high-hyperactivity group fell within the middle **Behaviour:** <u>CBCL delinquency</u>=correlated with number of movements during REM sleep. <u>Conduct disorder scale & measures of hyperactivity/immaturity & restless/disorganised behaviour</u> =correlated with number of total arousals & arousals from SWS. **Pubertal status:** Total sleep time and % SWS=differed between levels of puberty.
Storch et al (2009)	• Questionnaire (parents and children) Items from CBCL (n=6) & MASC (n=1) were	Sleep-related problems (SRP)	19.6% of sample=no sleep-related problems 19.7% of sample=4 or more SRPs Most common=nightmares & being overtired upon waking	**Gender:** Females=>total SRP **Age:** younger children=>total SRP **Tic severity:** Overall severity=not associated with SRP, but YGTSS motor

	combined to make composite measure			scale=-vely correlated with total SRP **QoL, internalising and externalising and anxiety=**Significantly related to number of total SRP **Psychopathology:** TS+anxiety dx=>SRP('sleeping less' & 'trouble sleeping')
Teive et al (2001)	• Review of clinic records	DSM-IV sleep problems	4 Pps='sleep problems'	N/A
Wand et al (1993)	• Questionnaire (Parents/parents+ children/children) Novel, modelled after the Ohio study of Tourette Syndrome	Frequency of sleep disturbance	Ratings of 'often' or 'sometimes' 66.4%=problems getting to sleep 31.3%=problems staying asleep 23.5%=sleepwalking	N/A

N/A=not applicable; Pps=participants; TS=Tourette syndrome; CTD=chronic tic disorder ADHD=attention deficit hyperactivity disorder; PLMS=periodic limb movements in sleep; SDB=sleep disordered breathing; REM=rapid eye movement sleep; SWS=slow wave sleep

5. Discussion

This review aimed to summarise existing studies of sleep difficulty in children with TS/CTD by focusing on the types and frequencies of sleep problems in this population and considering other factors that might affect sleep. Overall, a high prevalence of sleep difficulties in this group was identified, with sleep affected by factors such as comorbidity, medication use, age and gender. The studies varied in terms of methodology, sample characteristics and quality, with current findings based on a small and heterogeneous set of papers. The significance of these findings for understanding sleep problems in children with TS/CTD will be considered, along with suggestions for future research and potential clinical implications.

5.1 Types and frequency of sleep difficulties in children with TS/CTD

The results presented here support previous suggestions that children with TS/CTD experience more difficulties sleeping and have a higher prevalence of clinically significant sleep problems than typically developing control participants (Ghosh et al., 2014; Saccomani et al., 2005; Tieve et al., 2001). However, findings were less consistent about the type of difficulties experienced. Sleep initiation was not found to be a specific problem (Kirov et al., 2007b; Ghosh et al., 2014), although parents reported that before sleep children with TS/CTD felt anxious and required reassurance (Modafferi et al., 2016). Furthermore, whilst evidence for objective difficulties with sleep maintenance was inconclusive, parents tended to report that children with TS/CTD experienced fragmented sleep and sleep-interfering behaviours (e.g. nightmares, sleepwalking, bruxism, sleep-talking; Modafferi et al., 2016; Storch et al., 2009). Once asleep, PSG studies found that children with TS/CTD appeared to sleep less efficiently than healthy controls, although no relationship was reported between sleep efficiency and tic severity (Kirov et al., 2007b; Kostanecka-Endress et al., 2003). Nevertheless, increased levels of arousal and movement have been reported for some children with TS/CTD compared to healthy controls (Hashimoto et al., 1981). Across a number of studies no increased prevalence of specific movement disorders was found (e.g. PLMS; Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Stephens et al., 2007).

Thus, although this group clearly do experience a high level of sleep difficulty, the current evidence base does not seem to highlight a clear disorder-specific sleep pattern in children with TS/CTD. It could be that some of the sleep difficulties, including bruxism, movements during sleep and sleep talking echo tics exhibited by children during the daytime. It may be that sleep talking and bruxism are, at least in part, expressions of phonic tics while others (e.g. sleepwalking) may reflect high physiological arousal. However, to date, there are no studies that explicitly explore the relationship between specific daytime tics and

movements or arousals exhibited during sleep. This would therefore be a helpful direction for future research.

5.2 Association between sample characteristics and sleep problems

Age and gender both appeared to impact on sleep problem severity with females and younger participants being most at risk (Stephens et al., 2007; Storch et al., 2009). These relationships might be partially mediated by a third variable, such as tic severity and/or co-morbid psychopathology. Although the evidence for a relationship between tic severity and sleep was inconclusive overall (Kostanecka-Endress et al., 2003), increased motor tic severity was associated with poorer sleep in one study (Storch et al., 2009). Psychopathology also appeared related to sleep difficulties with some evidence that children with co-morbid anxiety or obsessive-compulsive symptoms might be most at risk (Storch et al., 2009; Modafferi et al., 2016). However, other studies found that number, rather than type of comorbidity, was related to sleep difficulty such that increased difficulties of any type were linked to increased sleep problems (Mol Debes et al., 2008).

In terms of externalising and behavioural difficulties, it appeared that difficulties with sleep maintenance, increased sleep stage latencies and REM-sleep changes were more clearly linked with ADHD than TS (Kirov et al., 2007a; 2007b). Notably, no significant changes in latency or duration of sleep stages or number of sleep cycles were associated with 'pure' tic disorders (Kostanecka-Endress et al., 2003). However, children with TS/CTD+ADHD showed changes to REM sleep latency and duration, and these differences were directly associated with severity and type of ADHD symptoms (Kirov et al., 2007a; 2007b). Externalising behaviours were positively associated with sleep problems in TS based on scores for ADHD characteristics such as hyperactivity and delinquency (Stephens et al., 2007). Furthermore, sleep-related movement disorders (PLMS and SDB) did not tend to present in children with TS-only, mostly occurring in those with comorbid ADHD (Kirov et al., 2007a; Kirov et al., 2007b; Kostanecka-Endress et al., 2003; Stephens et al., 2007). This may further support the link between ADHD and sleep in the context of TS/CTD.

Evidence for associations between sleep-related problems and medication-usage were unclear from the available evidence. This may partially be due to the lack of disclosure of medication status in 50% of included studies (Allen et al., 1992; Ghosh et al., 2014; Kostanecka-Endress et al., 2003; Modafferi et al., 2016). A possible hypothesis might be that links between sleep and medication-use in TS/CTD are mediated by pre-existing psychopathology. For instance, the association between anti-depressants and nightmares (Allen et al., 1992) could be due to the high levels of insomnia and nightmares in people with

depression (Nakajima, Inoue, Sasai, Okajima, Komada, Nomura et al., 2014) rather than TS/CTD specifically.

5.3 Methodologies of previous studies

The quality of included studies was mostly moderate, however, scores were highly heterogeneous. Only one study followed suggested best practice by using both an objective and subjective measure of sleep (Kostanecka-Endress et al., 2003). More studies used subjective than objective approaches (64% vs 36%), which may have biased the results through factors commonly affecting questionnaire studies (e.g. expectations; Danker-Hopfe, 2011). In support of this, differences were identified between studies using different types of measures. For instance, while children with TS/CTD did not experience objective difficulties with sleep maintenance (Ghosh et al., 2014), subjectively, parents reported that children with TS/CTD had significant difficulties staying asleep (Wand et al., 1993).

5.4 Limitations of previous research

The reviewed studies had various limitations. There was significant heterogeneity in all aspects of the studies discussed here so the present conclusions should be considered tentatively. Furthermore, the average quality rating for included studies was moderate, with the majority of studies individually scored as moderate or lower. This further impacts on the strength of the present conclusions. Many included studies used novel scales to assess sleep (sometimes referred to as 'franken-scales'; Gregory & Sadeh, 2016), which limits generalisability and comparability of findings across studies. Additionally, 85% of included studies recruited either partially or entirely through specialist clinics, which may mean that these participants have more severe TS/CTD than is seen in the general community (Robertson, 2000). Recruitment bias may therefore increase the chance and severity of difficulties, and thus potentially result in overestimation of rates of sleep disturbances compared to the wider population of children with TS/CTD. Finally, most studies were correlational in nature which does not allow consideration of the causality of sleep difficulties in TS/CTD.

5.5 Areas for further study

The limited evidence meeting criteria for the present review suggests a need for more research considering the nature of sleep difficulties in children with TS/CTD. It has been suggested that such a complex construct as sleep cannot be adequately assessed using a single approach (Gregory & Sadeh, 2016), however, as mentioned previously, very few studies in the present review did so. Future studies should therefore aim to use both subjective and

objective measures, along with questionnaires with multiple informants where possible. As well as giving a more holistic perspective on sleep, studies of this nature would provide clinically useful information that could be used to validate measures assessing perceptions of sleep by parents and children. Furthermore, only one included study explicitly assessed perceptions of the impact of sleep difficulties on everyday functioning (Ghosh et al., 2014). It would be helpful for more studies to consider characterising the daytime consequences of sleep problems, both objectively and subjectively, as this would further allow clinicians to consider functional domains that may be at risk in children with poor sleep.

Of note, none of the included studies used actigraphy. Five of the 14 studies included in this review used PSG, however, this provides a less naturalistic reflection of sleep (Sadeh, 2015). Children with TS/CTD also moved more during the night than controls (Hashimoto et al., 1981). Thus, night-time disturbance in children with TS/CTD may be most accurately explored using actigraphy, which relies on movement to assess sleep quality. Furthermore, future studies may benefit from including a range of standardised measures, such as the parent-report Children's Sleep Habits Questionnaire (CSHQ; Owens, Spirito & McGuinn, 2000), or the self-report Dysfunctional Beliefs about Sleep questionnaire (DBAS; Gregory, Cox, Crawford, Holland & Haravey, 2009). This would allow more generalizable and comparable conclusions to be made between studies and may generate information of greater clinical relevance.

Recruitment bias was also identified as a problem for many studies included in this review, with reliance on tertiary level clinical samples potentially overestimating the nature and degree of sleep disturbances. Thus, future studies should aim to explore sleep difficulties within more varied cohorts of TS/CTD patients, for instance by also recruiting through community clinics or charities. Furthermore, in line with the general male predominance of TS/CTD, females were under-represented in all samples. Although clinically-representative, this limits the strength of gender comparisons which may be of interest given that one study in the current review found females to be more at risk of sleep problems than males (Storch et al., 2009). Samples including a higher proportion of females would also allow hypotheses regarding the influence of hormonal changes on sleep in TS/CTD to be evaluated. Finally, although many studies in the present review noted ADHD prevalence, few considered other psychopathological comorbidities which are known to contribute to sleep problems in other clinical samples (e.g. depression; Devnani & Hedge, 2015). Thus, further evaluation of the potentially mediating effects of ADHD symptomatology, psychopathology and tics would also be of interest to help determine whether different patterns of sleep disturbance are seen in patients with different TS presentations (e.g. pure TS vs TS-plus vs full-blown TS).

The studies included in the present review focused on sleep at a single time-point. In future it may be interesting to conduct multiple sleep studies with a single cohort thus allowing a longitudinal exploration of sleep in TS/CTD. This may allow more causal inferences to be made about the impact of various factors on sleep which might inform future treatment and management options. In line with this, more researchers should consider specific approaches to managing sleep difficulties for children with TS/CTD. As previously outlined, interventions to improve sleep are usually pharmacological (Robertson, 2000). In general however, medications for sleep management have a mixed evidence base and are usually only recommended following failure of behavioural approaches (Kaczor & Skalski, 2016). It would therefore be helpful for future research to consider the efficacy of behavioural or psychotherapeutic sleep-focused interventions in children with TS/CTD to evaluate whether this might be a more efficacious and safe first-line treatment than psychopharmacology, and to identify any adaptations necessary for this patient group.

5.6 Limitations of the current review

The current findings should be considered within the context of various limitations. It is possible that some eligible studies could have been missed through limitations in the search strategy. Inclusion criteria was also fairly strict, excluding studies that were not peer-reviewed or written in English. This led to exclusion of a number of potentially-relevant abstracts, conference proceedings and posters. The heterogeneity of the evidence base and small number of included papers also compromises the reliability of conclusions which can be drawn here. Furthermore, eight of 63 excluded papers could not be accessed by the researcher. This may have biased the included sample towards articles in higher-impact, more recent, freely-accessible publications. However it should be noted that those excluded may have been unpublished due to being of low quality and thus may have had limited relevance for the present review. Taken together, these findings emphasise the need for more higher-quality studies to be conducted in future.

5.7 Clinical implications

Despite limitations of existing evidence and this review, some initial recommendations can be made for clinicians working with children with TS/CTD. It was consistently found that this cohort experienced significant sleep difficulties suggesting that these should be routinely screened for, and sleep hygiene information should be given to prevent or manage sleep difficulties early. Children with TS/CTD were said to experience pre-sleep anxiety (Modafferi et al., 2016), so may benefit from interventions to support anxiety management (e.g. relaxation), alongside sleep-focused advice. This could be especially helpful as children with TS/CTD and

comorbid anxiety were at particular risk of sleep problems (Storch et al., 2009). Further research around potential non-pharmacological intervention strategies and the daytime impact of sleep problems would be helpful in supporting clinicians to more confidently make recommendations to families, young people and others involved in their care about promoting good-quality sleep.

5.8 Conclusions

This review has summarised the current evidence regarding sleep difficulties in children with TS/CTD to explore whether any specific disturbances could be considered disorder-specific. The available research is limited, highly heterogeneous and mostly of moderate quality, but does suggest increased prevalence of sleep difficulties in TS/CTD compared to healthy controls. Some differences appear to be present between this and other clinical groups (e.g. ADHD), which may be indicative of different aetiology of sleep disturbance between conditions. However, at present, it does not appear that enough high-quality evidence exists to allow firm conclusions to be drawn regarding the disorder-specificity of sleep problems in TS/CTD. Limitations of the current review and evidence base, as well as suggestions for future research and clinical implications of these preliminary findings have been discussed with the hope of informing future work in this area.

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Nb: References marked with a * were full text articles reviewed but excluded from the final review according to the reasons outlined in the PRISMA flowchart in Figure 1.

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7. Appendices

Appendix 1: Quality Assessment Tool

Reference: Date of ax:

Criteria	Scoring System	Score
1. Are the aims and hypotheses of the study clearly described?	Yes No	1 0
2. Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 0
3. Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 0
4. Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 0
5. Number of study refusers stated?	Yes No	1 0
6. Medication status of participants reported?	Yes No	1 0
7. Tourette syndrome diagnosis confirmed?	Yes No	1 0
8. Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	1 0
9. Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 1 0
10. If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 0
11. Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	1 0
12. P values reported/significance of results discussed?	Yes No	1 0
		TOTAL: /14

Reference: Allen et al (1992) Date of ax: 10/12/216

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	**1** 0
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	**1** 0
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	**1** 0
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 **1** 0
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	1 **0**
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 10/14

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 **0**
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	1 **0**
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	1 **0**
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 4/14

Reference: Ghosh et al (2014) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 **0**
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	1 **0**
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	1 **0**
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	1 **0**
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 3/14

Reference: Hashimoto et al (1980) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	**2** 1 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	1 **0**
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 7/14

Reference: Kirov et al (2007a) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	**1** 0
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	**2** 1 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	**2** 1 0
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 11/14

Reference: Kirov et al (2007b) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	**1** 0
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	**2** 1 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	**2** 1 0
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 11/14

Reference: Kostanecka-Endress et al (2003) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	**1** 0
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	**2** 1 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	**2** 1 0
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 11/14

Reference: Modafferi et al (2016) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	**1** 0
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	1 **0**
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 **1** 0
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 8/14

Reference: Mol Debes et al (2008) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 **0**
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	**1** 0
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 7/14

Reference: Saccomani et al (2005) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	1 **0**
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 6/14

Reference: Stephens et al (2013) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	**1** 0
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	**1** 0
Medication status of participants reported?	Yes No	**1** 0
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	**2** 1 0
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 11/14

Reference: Storch et al (2009) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 **0**
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	**1** 0
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 7/14

Reference: Tieve et al (2001) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	1 **0**
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	1 **0**
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 **0**
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	1 **0**
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	**1** 0
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	**1** 0
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	1 **0**
		TOTAL: 4/14

Reference: Wand et al (1993) Date of ax: 10/12/2016

Criteria	Scoring System	Score
Are the aims and hypotheses of the study clearly described?	Yes No	**1** 0
Is the sample representative of the TS population?	Multiple recruitment sites/includes clinic and/or community participants Single site/specialist-clinic only	**1** 0
Did the sample include a Typically Developing comparison group?	Typically developing control group Only one sample or clinical control participants used	1 **0**
Is there an adequate sample size?	Power analysis conducted and reported or sample size discussed No clear power calculations or sample size not mentioned	1 **0**
Number of study refusers stated?	Yes No	**1** 0
Medication status of participants reported?	Yes No	1 **0**
Tourette syndrome diagnosis confirmed?	Yes No	1 **0**
Validated measure of sleep used?	Validated questionnaire or analysis parameters Novel/unclear	1 **0**
Sample adequately characterised in terms of mean IQ, age and gender distribution?	All three reported Only two reported Only one reported	2 **1** 0
If >1 group, were they matched for age, IQ and gender?	All three Only two Only one/not clear/not applicable	2 1 **0**
Comorbid neurodevelopmental and/or psychiatric conditions screened for?	Yes No	**1** 0
P values reported/significance of results discussed?	Yes No	**1** 0
		TOTAL: 6/14

Empirical Research Project

A naturalistic study exploring the association between sleep and cognition in children with tic disorders

Supervised by:

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1. Abstract

Objectives: Sleep difficulties are often assumed to be common in children with tic disorders such as Tourette syndrome (TS) and may be related to neurobehavioural and psychopathological outcomes in this group (Modafferi, Stornelli, Chiarotti, Cardona, & Bruni, 2016; Kirov, Brand, Banaschewski & Rothenberger, 2017). However, existing research into associations between these functional domains in this clinical group is limited and highly heterogeneous. This study will compare naturalistic sleep patterns and possible factors associated with disturbed sleep in a group of children with tic disorders and a matched typically developing control group. It will also consider relationships between sleep, psychopathology and learning in these groups and explore the process of overnight information consolidation as a potential mechanism for altered sleep-dependent learning.

Methods: Sleep was assessed in a sample of 32 young adolescent males with tic disorders (n=16) and age-, gender- and IQ-matched typically developing controls (n=16) using actigraphy. Participants and their parents completed a set of clinical questionnaires to measure psychopathology and children were administered a comprehensive neuropsychological battery to assess cognitive functioning. Overnight information consolidation was assessed using a novel set of computerised tasks which were completed by participants before and after a single night of sleep.

Results: Sleep was highly variable in the clinical group but overall was not significantly different between groups. For children with TS, longer onset latency was associated with significantly more symptoms of depression and panic disorder and poorer learning performance on a verbal memory task than controls. Comparatively, no significant associations emerged between sleep, psychopathology and overnight learning in the control group. Trends in the data are suggestive of different overnight learning profiles and different associations between consolidation and underlying cognitive skills between groups.

Conclusions: Differences in relationships with psychopathology, patterns of learning and associations with neurocognitive abilities suggest the possibility of different mechanisms underlying associations between sleep and daytime functioning between these groups. The importance of these findings in supporting systematic screening of sleep difficulties alongside assessment of psychopathological and learning profiles in children with TS are discussed.

2. Introduction

2.1 Sleep Overview

Sleep is an active, restorative state said to be "of the brain, by the brain and for the brain" (p. 487; Anderson, 2015). Sleep quality and quantity is determined by interacting physiological, chronobiological and neurological processes (Beebe, 2012). Regulation of sleep is determined by the balance between the wakefulness-related circadian drive (known as 'process C') and the sleep-facilitating homeostatic drive ('Process S'; Sinha, Jhaveri & Banga, 2015). Neurologically sleep-wake regulation begins with arousal-promoting glutamatergic, cholinergic, noradrenergic, dopaminergic and histaminergic projections from the brainstem and hypothalamus which ascend either directly or via the thalamus into the cortex. Concomitantly gamma-aminobutyric acid (GABA)-ergic hypothalamic projections are deactivated which has an excitatory effect on the sympathetic nervous system. This dynamic balance of systems is stabilised by hypothalamic orexin/hypocretin-producing neurons (Beebe, 2012). During the initial stages of sleep (N1 and N2) hypothalamic GABA pathways become more active, inhibiting the arousal-related projections as parasympathetic activation slows heart rate, blood pressure and respiration. As the third sleep stage (slow wave sleep (SWS)) begins, thalamo-cortical-thalamic circuits organise slow, synchronised, rhythmic firing of large neuronal groups. The fourth sleep stage (rapid eye movement (REM) sleep) follows activation of cholinergic systems with simultaneous suppression of aminergic and histaminergic pathways. This results in heightened thalamic, limbic and posterior cortical activity, continued deactivation of anterior cortical areas and inhibition of motor signals (Beebe, 2012). These stages occur in repeated cycles during a sleep period. Sleep is therefore an extremely vulnerable and complex process associated with multiple interacting systems, changes to any of which can cause sleep disturbance.

Sleep patterns change throughout development with a significant shift at the transition from childhood to adolescence; this is linked to hormonal and central nervous system (CNS) development, lifestyle factors (e.g. electronic media usage) and a tendency towards 'eveningness' (Barclay & Gregory, 2014; MacLean, Fitzgerald & Waters, 2015; de Bruin, van Run, Staaks & Meijer, 2017). At this developmental stage, inconsistencies also occur across school terms and holidays with the latter being characterised by increased autonomy and often subsequently less routine sleep (Danker-Hopfe, 2011). Sleep maturation is highly inter- and intra-individually variable and, due to its reliance on CNS development, occurs differently across clinical and healthy populations (Meltzer, 2017).

2.1.1 Functions of sleep

Despite being a time of relative physical inactivity, during sleep the brain actively processes and stores information (Tesler, Gerstenberg & Huber, 2013). Key functions of sleep are to support emotional regulation and facilitate learning (Vriend, Davidson, Rusak & Corkum, 2015). Insufficient or disturbed sleep can therefore significantly affect social, academic and neurobehavioural functioning (Ashworth, Hill, Karmiloff-Smith & Dimitriou, 2014).

2.1.2 Sleep and emotional functioning

A key role of sleep is to support emotional processing and regulation. In line with this, sleep disturbance is a central feature of many psychological disorders including depression (Chorney, Detweiler, Morris & Kuhn, 2008), anxiety (Hansen, Skirbekk, Oerbeck, Wentzel-Larsen & Kristensen, 2014) and obsessive compulsive disorder (OCD; Paterson, Reynolds, Ferguson & Dawson, 2013). The relationship between sleep and psychopathology varies between disorders but is generally assumed to be bidirectional and moderated by neuropathological and behavioural mechanisms (Basseti, Ferini-Strambi, Brown, Adamantidis, Benedetti, Bruni et al., 2015). Neurologically, shorter sleep duration contributes to enhanced reactivity of regions involved in emotional processing, including the amygdala and insula, along with weakened connections to regulatory areas of the prefrontal cortex (PFC; Reidy, Hamann, Inman, Johnson & Brennan, 2016). Furthermore, changes in the functioning of neurotransmitters dopamine (DA) and serotonin (5-HT) are implicated in a range of neurodevelopmental and psychiatric conditions and also affect the circadian system. This reinforces the intimate neurobiological link between sleep and emotional functioning (Harvey, Murray, Chandler & Soehner, 2011).

Children with psychiatric and developmental conditions also exhibit disorder-specific behaviours that impact on sleep duration and quality (Ramtekkar & Ivanenko, 2015). For instance, children with autism spectrum disorder (ASD) often show delayed sleep onset due to ritualistic tendencies, arousal dysregulation and impaired self-soothing (Beebe, 2012). Attention deficit hyperactivity disorder (ADHD) is also characterised by sleep onset difficulties but these typically present as bedtime resistance linked to restlessness and oppositionality (Cortese, Faraone, Konofal & Lecendreux, 2009). Sleep difficulties can be further inadvertently reinforced by parental accommodations (e.g. co-sleeping; Thompson-Hollands, Kerns, Pincus & Comer, 2014) and systemic factors (e.g. family conflict) which are often elevated in families where children have disabilities (El-Sheikh, Kelly, Bagley & Wetter, 2012).

2.1.3 Sleep and learning

As outlined, another key task for the sleeping brain is to consolidate information; that is to facilitate learning through strengthening memory traces acquired during waking hours (Astill, Van der Heijden, Van IJzendoorn & Van Someren, 2012; Born & Wagner, 2009). In typically developing children consolidation occurs during SWS and REM sleep, with the former supporting episodic declarative memories and the latter being important for emotional consolidation and regulation (Walker, 2009; Weisner, Pulst, Krause, Elsner, Baving, Pedersen et al., 2015). The association between sleep and learning in non-clinical children is affected by a range of individual (e.g. age, socio-economic status, ethnicity), task-related (e.g. complexity, salience) and situational factors (e.g. motivation, arousal level; Sadeh, Gruber & Raviv, 2002; McMakin & Alfano, 2015; Philbrook, Hinnant, Elmore-Staton, Buckhalt & El-Sheikh, 2017). Despite various theories of consolidation being proposed (e.g. 'active systems consolidation' Born & Wilhelm, 2012; 'synaptic-homeostasis'; Tononi & Cirelli, 2003) the mechanisms underlying this process remain insufficiently understood.

Associations between sleep duration and volumes of neural regions such as the hippocampus reinforce the role of sleep in learning (Taki, Hashizume, Thyreau, Sassa, Takeuchi, Wu et al., 2012). The hippocampus is often activated alongside the amygdala during sleep (Diekelman, Wilhelm & Born, 2009). This supports the notion that emotional memories are preferentially consolidated over those which are neutral. Regions of the PFC are also implicated in consolidation through 'marking' memories for recall and facilitating encoding, which relies on dopaminergic regulation of neural plasticity (Berry, Cervantes-Sandoval, Chakroborty & Davis, 2015). Correspondingly, consolidation appears to function differently in individuals with altered DA transmission and PFC development (e.g. ADHD; Prehn-Kristensen, Göder, Fischer, Wilhelm, Seeck-Hirschner, Adenhoff & Baving, 2011). For instance, initial studies have found that compared to typically developing children, in ADHD, salient (i.e. emotionally valenced or rewarding) information tends not to be preferentially consolidated over neutral stimuli during sleep (Wiesner, Molzow, Prehn-Kristensen & Baving, 2017; Prehn-Kristensen, Munz, Molsow, Wilhelm, Weisner & Baving, 2013). Furthermore, REM sleep duration has been found to be associated differently with measures of cognitive and emotional functioning in children with developmental disorders and typically developing peers (e.g. ADHD, Tourette syndrome (TS); Kirov et al., 2017). As REM sleep is known to support consolidation (Weisner et al., 2015), this may occur through changes in this underlying mechanism. However, despite initial studies into this process in ADHD, to the author's knowledge overnight consolidation has not yet been explicitly explored in children with TS.

Thus, sleep disturbances have wide-ranging effects on everyday functioning in typically developing children and may exacerbate or add to functional disability in clinical populations.

Understanding and managing sleep problems is therefore being increasingly recognised as a crucial factor in enhancing children's wellbeing and supporting optimal development (Harvey et al., 2011; Maski & Kothare, 2013).

2.1.4 Sleep assessment

The complex neurobehavioural nature of sleep makes it challenging to accurately assess (Gregory & Sadeh, 2012). Questionnaires are a time- and cost-effective way to gather information about perceptions of sleep from multiple respondents. They are useful for identifying sleep-related concerns and understanding bedtime habits (Mouthon & Huber, 2015). However their inherently subjective nature makes them unsuitable for diagnosis of sleep disorders, or characterising sleep architecture (Danke-Hopfer, 2011). For this, objective techniques, such as the 'gold standard', polysomnography (PSG) should be used. PSG involves laboratory monitoring, usually over two nights, and generates extremely detailed information about sleep physiology. However, due to the requirement to sleep in a laboratory during monitoring, PSG is not especially representative of natural sleep patterns (Sadeh, 2015). An alternative objective approach is actigraphy. This uses an accelerometer to assess movement and light levels from which habitual sleep-wake patterns can be determined. Actigraphic recordings are typically collected for days or weeks and devices can be used within participants' own homes (Mouthon & Huber, 2015). Although not precise enough to allow diagnosis of sleep disorders or reliably assess sleep quality, actigraphy is useful for identifying sleep quantity and general disturbance in children (Galland, Meredith-Jones, Terrill & Taylor, 2014; Danker-Hopfer, 2011). Accuracy is enhanced by using sleep logs to validate actigraphy data and determine artefacts (e.g. device removal; Mouthon & Huber, 2015). Although it is clearly important to assess perceptions of sleep (Honomichl, Goodlin-Jones, Burnham, Gaylor & Anders, 2002), subjective and objective measures tend to correlate weakly and the latter is generally considered more accurate (Markovich, Gendron & Corkum, 2015; Kushnir & Sadeh, 2013).

2.2 Tourette syndrome

Gilles de la Tourette syndrome (TS) is a complex neuropsychiatric condition characterised by the presence of multiple motor tics and at least one phonic tic that have been present for at least one year, begin before 18 years of age and are not caused by medications or health conditions (DSM-V; American Psychiatric Association, 2013). Tics are brief, sudden movements or sounds sometimes preceded by a premonitory 'urge' (Brandt, Beck, Sajin, Baaske, Bäumer, Beste et al., 2016). They are suggestible, suppressible and vary in frequency (Kumar, Trescher & Byler, 2016). Tics usually first appear in childhood and peak in severity

around 10-12 years. They often improve during adolescence and can disappear by adulthood (Bloch & Leckman, 2009; Freeman, Fast, Burd, Kerbeshian, Robertson, & Sandor, 2000). Tics can be simple or complex. 'Simple' tics involve single muscles or sounds (e.g. eye-blinking, coughing) while those considered 'complex' include multiple muscles or body parts, speaking phrases or strings of sounds. Whereas simple tics are clearly purposeless, complex tics may appear purposeful (e.g. grooming actions) and can present as copying other people's movements ('echopraxia'), copying speech ('echolalia') or making obscene gestures or comments ('copraphenomena'). Overall prevalence estimates for TS in childhood are around 0.77% and it is approximately four times more common in males than females (Knight, Steeves, Day, Lowerison, Jette & Pringesheim, 2012; Freeman et al., 2000).

TS is approximately 60% heritable (Matthews & Stern, 2016) and although few single risk genes have been identified (Richer & Fernandez, 2015), those related to DA transmission are often altered (Du, Chiu, Lee, Wu, Yang, Hsu et al., 2010). DA is not the only neurotransmitter implicated in TS pathophysiology, with evidence also supporting roles for noradrenaline, glutamate, 5-HT, histamines and GABA (Nordstrom, Bittner, McGrath, Parks & Burton, 2015; Leckman, Bloch, Smith, Larabi & Hampson, 2010). However DA has a substantial evidence base due to the effectiveness of its antagonists in managing TS symptoms (Paschou, Fernandez, Sharp, Heiman & Hoekstra, 2013; Shprecher, Schrock & Himle, 2014). Although the nature of its role in TS is debated (Buse, Schoenefeld, Münchau & Roessner, 2013) patients show delayed maturation of the DA-mediated PFC as well as alterations across regions linking frontal to subcortical areas (Yaniv, Benaroya-Milshtein, Steinberg, Ruhrrman, Apter & Lavidor, 2017; Worbe, Malherbe, Hartmann, Pelegrini-Isaac, Messe, Vidailhet et al., 2012). Neurological changes are thought to occur across interacting cortico-striatal-thalamo-cortical (CSTC) circuits (Robertson, Eapen, Singer, Martino, Scharf, Paschou et al., 2017). These include a premotor-putamen circuit associated with habitual-behavioural functions, a goal-directed ventromedial PFC-caudate nucleus circuit and a limbic circuit, which collaboratively implicate a network of regions associated with inhibition, habit formation and reward in TS pathophysiology (Mink, 2001). These structural differences are accompanied by aberrant patterns of neural functioning, with a well-supported hypothesis attributing tics to hypoactivity in striatopallidal neurons which impairs inhibition of GABA-ergic basal ganglia-generated motor patterns (Felling & Singer, 2011). This inhibitory impairment becomes habitual following reinforcing DA-release due to caudate and PFC hyperactivity (Leckman et al., 2010). The link between tics and inhibitory control is further supported by neurocognitive findings of impaired verbal and motor inhibition in TS (Matthews & Stern, 2016).

Although impaired inhibition of overactive motor networks appears central to TS pathophysiology, this does not explain tic fluctuations or failures in suppression during times of stress or stimulation (McGuire, 2016; Jackson, Draper, Dyke, Pépés & Jackson, 2015; Ruhrman, Gev, Benaroya-Milshtein, Fennig, Krispin, Apter & Steinberg, 2017). One explanation of this links tic fluctuations to homeostatic changes which are reflected in TS patients' heightened stress-related cortisol release and hypothalamic-pituitary-adrenocortical (HPA) axis hyperactivity (Godar & Bortolato, 2016; Buse, Kirschbaum, Leckman, Münchau & Roessner, 2014; Corbett, Mendoza, Baym, Bunge & Levine, 2008).

2.2.1 TS and comorbidity

Overall, therefore, TS is a highly complex psychophysiological syndrome (Lavoie, Leclerc & O'Connor, 2013), reflected in its position "at the border between neurology and psychiatry" (p 20; Cavanna, Servo, Monaco & Robertson, 2009). Attempts to make TS more comprehensible have led clinicians and researchers to subtype the condition. A common distinction is between 'Pure TS' (tics only), 'TS plus' (TS accompanied by echo- and copraphenomena) and 'Full Blown TS' ('TS plus' with comorbid neurodevelopmental and/or psychiatric difficulties; Robertson & Baron-Cohen, 1998). Pure TS is considered 'the exception, rather than the rule' (Leckman, Bloch, Scahill & King, 2006) with common comorbidities including ADHD, OCD and depression (Ferreira, Pio-Abreu & Januario, 2014; Cavanna et al., 2009). Comorbid conditions often prompt TS patients to seek medical attention (Robertson, 2000) and lead to reduced quality of life (QoL) than is reported by those without comorbidities (Eapen, Snedden, Črnčec, Pick & Sachdev, 2016; Hesapçıoğlu, Tural & Kandil, 2014).

The relationship between TS and comorbidity is complex and, like tics themselves, likely to be multifactorial. Neurochemical and neuroanatomical changes, such as DA and CSTC abnormalities, are shared across TS and other conditions (e.g. depression; Peters, Dunlop & Downar, 2016; Grace, 2017). However the experience of having tics also directly impacts on wellbeing, as 'pure TS' patients experience emotional and social difficulties and tic severity is linked to low mood and suicidal thoughts (Zinner, Conelea, Glew, Woods & Budman, 2014; Storch, Hanks, Mink, McGuire, Adams, Augustine, Vierhile, Thatcher et al., 2015). Growing awareness of the significant psychosocial burden associated with TS has stimulated research specifically into 'plus' forms of the condition, as well as factors influencing wellbeing and health related-QoL (HR-QoL) across disorder subtypes (Sprecher et al., 2014). It is hoped that this will facilitate development of a fuller understanding of TS and inform targeted therapeutic interventions to improve functional outcomes for patients and families (O'Hare, Helmes, Reece, Eapen & McBain, 2016).

2.2.2 Sleep in TS

Since the initial conceptualisation of TS, patients' sleep has been of clinical interest (Konofal, Karroum, Montplaisir, Derenne & Arnulf, 2009). Despite suggestions that sleep is not always disturbed in 'pure TS' (Freeman et al., 2000) and that tics are ameliorated during sleep (Hashemiyoon, Kuhn & Visser-Vanderwalle, 2017), clinically significant sleep disorders have been reported in up to 65% of TS samples (Ghosh, Rajan, Das, Datta, Rothner & Erenberg, 2014). Studies relying on parent-report have found significant pre-sleep anxiety (Modaferri et al., 2016) as well as fragmented sleep and frequent sleep-interfering behaviours (e.g. bruxism, sleepwalking) in this group (Modafferi et al., 2016; Storch, Milsom, Lack, Pence, Geffken, Jacob et al., 2009). PSG studies have typically found children with TS to sleep less efficiently and move more overnight than healthy controls (Kirov, Kinkelbur, Banaschewski, & Rothenberger, 2007; Kostanecka-Endress, Banaschewski, Kinkelbur, Wullner, Lichtblau, Cohrs et al., 2003; Hashimoto, Endo, Fukuda, Hiura, Kawano, Suzue et al., 1981).

Although some studies have concluded that sleep difficulties in TS are due to comorbid conditions (e.g. ADHD; Allen, Singer, Brown & Salam, 1992) or additional factors (e.g. medications, Ayalon, Hermesh & Dagan, 2002; Cavanna, Selvini, Termine, Luoni, Eddy & Rickards, 2012), others have suggested that sleep disturbance is a central aspect of TS (Kirov et al., 2007). In support of this, some studies have linked tic severity to sleep disturbance (Kirov et al., 2007) and others have observed sleep improvements following pharmacological treatment of tics (Arana-Lechuga, Sanchez-Escandon, Santiago-Trevino, Castillo-Montoya, Teran-Perez & Velazquez-Moctezuma, 2008). TS patients can display tic-like movements and other motoric arousals during sleep and this may reflect overnight consolidation of tic-related motor programs (Kirov, Becker & Rothenberger, 2014; Kirov et al., 2007; Cohrs, Rasch, Altmeyer, Kinkelbur, Kostanecka, Rothenberger et al., 2001). Presence of overnight movements could also implicate physiological hyper-arousal in the aetiology of both tics and sleep disturbance (Modafferi et al., 2016). Furthermore, the importance of neural regions across the CSTC network and reliance on physiological homeostasis for sleep, both of which are impaired in TS, could contribute to disturbed sleep in patients. Attempts have therefore been made to characterise and understand sleep difficulties in TS. However the existing evidence base is highly inconsistent and limited, being based primarily on small, clinically-recruited samples (Hibberd et al., 2017). Furthermore to the author's knowledge all previous studies have assessed sleep using PSG or questionnaires with none using the naturalistic objective approach of actigraphy.

Exploration into the functional impact of poor sleep in TS is also only just beginning. Initial studies have found associations between sleep disturbances and internalising and

externalising difficulties in patients (Storch et al., 2009; Freeman et al., 2000). From these initial findings a reciprocal relationship has been proposed between sleep, tics and daytime functioning. Within this relationship, tics could contribute to sleep difficulties which would negatively affect psychosocial and neurobehavioural functioning, in turn increasing tic occurrence and further impairing functioning (Kirov et al., 2014). Partial support for this is provided by a recent study of children with TS which confirmed a positive association between sleep disturbance and psychopathology (Modaferri et al., 2016). These authors also extended the previous proposal by finding links between particular psychological symptoms and sleep profiles in this group. Specifically, anxiety was linked to sleep-related movement while both depression and OCD were associated with sleep initiation difficulties (Modaferri et al., 2016). However, this study relied on parent-report of sleep, which as previously outlined is not the most accurate method of assessment (Kushnir & Sadeh, 2013). Furthermore, the authors did not consider the impact of reported sleep problems on areas of functioning other than psychopathology. Considering recent findings of opposing associations between REM sleep duration and neurobehavioural functioning in children with TS/ADHD and healthy controls (Kirov et al., 2017) as well as suggestions of altered processes of consolidation in ADHD (Weisner et al., 2017), it would be helpful to directly explore both consolidation and general emotional and cognitive functioning alongside sleep in a TS sample. It is hoped that this will give more information about sleep disturbance and its potential functional implications in TS as well as some insight into a possible mechanism for different learning processes in this group (i.e. altered consolidation)

2.3 Study rationale, aims and hypotheses

The present study therefore aims to add to the growing body of literature on sleep in children with TS in several ways. Firstly, it will be the first study to the author's knowledge to objectively assess naturalistic sleep using actigraphy in this group. Secondly, based on the work of Kirov et al (2014) and Modaferri et al (2016), relationships will be explored between sleep disturbance and symptoms of a range of psychological disorders, as assessed by the Revised Children's Anxiety and Depression Scale (RCADS; Chorpita, Moffitt & Gray, 2005). Thirdly, based on initial suggestions of different associations between sleep and learning in TS and healthy samples (Kirov et al., 2017) we will use a set of novel cognitive learning tasks to explore associations between sleep and consolidation in these groups.

The study has three primary hypotheses:

1. Children with TS will have more sleep difficulties than typically developing control participants.

2. Sleep difficulties will be associated with symptoms of various psychological disorders in both groups but this effect will be more pronounced in TS.
3. Increased sleep disturbance will be associated with poorer performance on novel overnight cognitive learning tasks for both the TS and control groups. It is unknown whether this effect will differ between groups so this will be explored.

3 Method

3.1 Ethical approval

This study was approved by King's College London Psychiatry, Nursing and Midwifery Research Ethics Committee (REC) on 23/12/2015 (Study Reference: HR15/162278; Appendix 7). Approval was granted by the Health Research Authority REC Camden and King's Cross committee on 15/05/2016 (Study reference: 16/LO/0393; Appendix 8).

3.2 Power analysis

Power analysis was conducted a priori using the software GPower. To our knowledge no existing studies have explored both sleep and learning using a between-groups design in either children or adults with TS. The most closely-related studies in samples of children with TS have considered sleep disruption. With this in mind using the effect of sleep vs wakefulness for the effect of memory consolidation in typically developing children (Wilhelm, Diekelmann & Born, 2008) requires a sample size of 12 participants, with power (1-β) at 80% and α at .05, two tailed. For the effect of disrupted vs non-disrupted sleep in TS requires a sample size of 32 participants (16 per condition) based on the mean number of awakenings after sleep onset (Kostanecka-Endress et al, 2003) with power (1-β) set at 0.80 and α at .05, one-tailed.

3.3 Recruitment and participants

TS participants were recruited through the Tics and Neurodevelopmental Movements (TANDeM) clinic at Evelina London and online advertisements from the charity 'Tourette Action'. Control participants were recruited through advertisements on the King's College research circular, a listing on the Guy's and St Thomas' Hospital Foundation Trust intranet and by contacting community organisations and schools (see Appendix 1 for recruitment letter). Following initial expression of interest, participants were screened according to the inclusion criteria. Once eligibility was established children and parents were sent information sheets. Those recruited through the TANDeM clinic were sent sheets A to C (Appendix 2) while others were sent the relevant sheets from D to G (Appendix 3). Interested children and parents were then sent consent forms (Appendices 4 and 5) to sign. After giving informed consent a letter was sent to the General Practitioner (GP) of participants recruited through the TANDeM clinic to inform them of their patient's participation (Appendix 6).

3.3.1 Inclusion and exclusion criteria

Participants were included if they were male, aged between 11 and 14 at the time of the study and had a current diagnosis of TS or CTD. Exclusion criteria included a diagnosis of ASD, Learning Disability (defined as a full-scale intelligence quotient (FSIQ) score <70), or changes to any prescribed medications within three months of participating. If children took Melatonin to aid sleep, they were asked not to do so for the study period. Participants were

not excluded on the basis of presence of comorbid ADHD as, due to the high comorbidity between ADHD and TS, this was not felt to be clinically-representative.

3.4 Materials and measures

3.4.1 Tic severity

Tic severity was measured using the Yale Global Tic Severity Scale (YGTSS; Leckman, Riddle, Hardin, Ort, Swartz, Stevenson & Cohen, 1989). This semi-structured clinician-rated instrument assesses the nature of tics historically and currently. It also includes ratings of the number, frequency, intensity, complexity and interference of motor and phonic tics in categories scored from 0 (none/absent) to 5 (e.g. always present/severe intensity) giving a range of 0-25 for overall motor and phonic tic severity and a total tic severity score of 0-50. The functional impairment caused by tics is also scored on a 0-50 scale. Global severity can be calculated by combining total tic score with the impairment rating giving an overall score from 0 to 100. The YGTSS is widely accepted as gold standard for paediatric tic assessment due to high internal consistency and stability of scores over time (Storch, Murphy, Geffken, Sajid, Allen, Roberti & Goodman, 2005).

3.4.2 Sleep

Participants wore an actigraph (Phillips Actiwatch Spectrum Pro) on their non-dominant wrist continuously for 14 days with an epoch length of 30 seconds. Outputs were downloaded from each watch onto a corresponding software package (Actiware software package v 6.0) for analysis. Measures calculated were sleep onset latency, sleep efficiency percentage (sleep duration/sleep period) and minutes of wake after sleep onset (WASO). The researcher (CH) was trained in actigraphy administration and analysis by technicians from the Evelina London sleep clinic prior to the study commencing. During the first contact with the researcher, participants were given the actiwatch along with a set of information sheets and a sleep diary (appendix 9). Participants were instructed to keep the diary for the duration of the sleep study. The measure used was developed by the Evelina London sleep clinic and is routinely used clinically to aid actigraphy interpretation.

3.4.3 Overnight learning

Overnight learning was assessed using the 'Sleepsuite' games; this set of novel iPad-based tasks were developed by a member of the research team (PG). The games were designed specifically to assess consolidation, while being engaging and enjoyable for children. They are currently being validated in various clinical and non-clinical populations.

Three games were selected for the current project; these included a verbal learning task (*the 'Animals' task*), a continuous performance task (CPT; *the 'Balloons' task*), and a

spatial learning task (*the 'Mazes' task*). The games are introduced by a fictional character, 'Lou', who guides players through each task (see Figure 1 for graphics).

*Animals tas*k**:** Participants learn the names of 12 animals (e.g. 'Perla the owl'). They are asked to recall these after a twelve minute break. The task is assessed based on recall after this interval, and then following a period of sleep.

Balloons task (Rosenberg-Kima & Sadeh, 2010): In this CPT participants must detect target stimuli among a set of distractors. The game shows a lake from which 'balloons' filled with pictures of a diverse set of children's faces showing different expressions emerge. Participants must 'pop' balloons with their finger according to certain rules designed to assess consolidation of emotion and gender information:

Balloons emotion: Players are instructed to 'pop all of the happy faces'

Balloons gender: Instructions are to 'pop all of the girls' faces'

Stimuli presentation speeds up during the task. The task is the same pre- and post-sleep and is scored on the number of commission errors made during each trial.

Mazes task: (Nguyen, Tucker, Stickgold & Wamsley, 2013) Participants must memorise a 2D map, which they must then follow within a 3D maze to reach a ball of fire; the task is

Figure 1: Graphics for the Sleepsuite Animals, Balloons and Mazes tasks

scored based on navigation speed.

3.4.4 Cognition

To check for any differences in cognitive functioning between groups, various domains of cognition were assessed using a standardised battery of neuropsychological measures. The battery was designed to give a comprehensive overview of intellectual functioning. A summary of the battery is displayed in Table 1 and a description of each measure is included in Appendix 10.

Table 1: Cognitive test battery

Measure	Domain of interest
Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II; Wechsler, 2011) 2 subtest version	IQ
Cancellation (subtest from Wechsler Intelligence Scale for Children, 4th edition; WISC-IV; Wechsler, 2003)	Processing speed & selective attention
Block Recall (subtest from Working Memory Test Battery for Children; WMTB-C; Gathercole & Pickering, 2001)	Visuo-spatial working memory
Digit Span (subtest from WISC-IV; Wechsler, 2003)	Verbal working memory
California Verbal Learning Test for Children (CVLT-C; Delis, Kramer, Kaplan & Ober, 1994)	Verbal learning and memory
Colour-word interference (subtest from Delis-Kaplan Executive Functioning System; DKEFS; Delis, Kaplan & Kramer, 2001)	Verbal inhibition
Walk, don't walk (subtest from Test of Everyday Attention for Children; TEA-Ch; Manly, Robertson, Anderson & Nimmo-Smith, 1998)	Motor inhibition
Grooved Pegboard Test (Klove, 1963)	Visuo-motor coordination
Blending Words (subtest from Comprehensive Test of Phonological Processing, second edition; CTOPP-2; Wagner, Torgesen, Rashotte & Pearson, 2013)	Phonological Awareness

3.4.5 Emotional and behavioural functioning

Perception of emotional functioning and quality of life was assessed with a range of standardised questionnaires administered to young people and their parents or guardians. Parents of TS participants were also administered the YGTSS (described in section 3.4.1) to assess tic severity. An overview of the questionnaires administered is included below (Table 2) and further information about each can be found in Appendix 11.

Table 2: Questionnaire battery

Measure	Respondent and domain
Conners 3rd edition (Conners, 2008)	Parent report ADHD symptoms
Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997)	Self-report and parent report General wellbeing
Revised Children's Anxiety and Depression Scale (RCADS; Chorpita et al., 2005)	Self-report and parent report Anxiety and depression symptoms
Paediatric Quality of Life (PedsOL; Varni, Seid & Rode, 1999)	Self-report and parent report General quality of life

3.5 Procedure

Once children and parents had provided written consent to participate in the study, the researcher arranged to visit participants at home or school to administer the cognitive battery and questionnaires. For this reason, participants were only recruited if they lived in a location accessible to the researcher (i.e. in the south of England). Participants were given the

actiwatch and accompanying paperwork (see Appendix 9) at this appointment and instructed to wear the actiwatch for 14 days and nights. If available, participants were given an iPad and instructions to complete the Sleepsuite tasks before and after a single night of sleep. If an iPad was not available at this time, one was sent to participants as soon as possible. Every participant completed the tasks within one month of their sleep study. Following the final study day all equipment was collected from participants and the data was scored and analysed by the researcher.

3.6 Statistical analysis

All data analysis for this study was completed using SPSS for windows (v23).

4. **Results**

4.1 Preliminary analyses

The data was screened to check for normality, to look for outliers (mean ± ≥3.29 (z score)) and to examine missing values. Normality was inspected with histograms and Q-Q plots. Sleepsuite data was further screened and any values considered to represent non-compliance (extreme or implausible scores) were excluded from this section of the analysis. These were determined by studying z-scores and box plots to look for outlying scores. Based on recommendations from previous uses of the *Balloons* task by the developer (PG) this measure was further assessed for noncompliance. Recommendations are that values considered to reflect implausible performance (high commission + low omission errors) should be excluded. Three control participants were excluded from *Balloons* analysis for implausible scores but could be included in the remainder of the analysis. Homogeneity of variance was assessed with Levene's test before using parametric tests.

4.2 Sample characteristics

32 young adolescent males participated in the present study, this sample included a group with TS (n=16) and a group of typically developing control children (n=16). 51 additional children expressed interest in participating but could not be included for the following reasons: diagnosis of ASD/LD (n=11), outside age range (n=12), female (n=3), lived too far away (n=25). Following this careful initial screening by the researcher, the remaining 32 participants all met inclusion criteria so could be included in the analysis. Characteristics of the sample are displayed in Table 3. The groups did not differ in age *[t(30)=.165, p=.870]*, but there were differences in the time they participated in the two week sleep study. More TS than control children took part during term-time (68.8% vs 31.3%). Half of the control group participated during both term and holiday (i.e. a week of holiday and a week of term; 50% of controls vs 25% of TS)[2]. TS participants were recruited in equal numbers from the TANDeM clinic at Evelina London (50%) and through the charity Tourette Action (50%), while over half of control participants (56%) were recruited through schools[3].

4.2.1 Tic severity

For the TS group, tic severity was assessed using the YGTSS. Tic severity ranged from 6-42 with a mean score within the 'moderate' range of 26.2. Overall impairment scores ranged from 6-82, with a mean of 50.2, which is also considered moderate. Independent samples t-tests

[2] Chi-square analysis showed no significant differences in time of participation between groups ($x^2(2, 32)=3.36$, p=.186).

[3] Independent samples t-tests showed no significant difference between actigraphy results dependent on recruitment source.

showed no significant difference in overall tic severity or associated functional impairment between participants recruited from the clinic as compared to charity recruits (see appendix 12 for full scores).

Table 3 Sample demographics

		TS (n=16) Range (M, SD) or n(%)	**Control** (n=16) Range (M, SD) or n(%)
Age (years)		11-14 (12.3,1.25)	11-14 (12.2,0.85)
Time of participation	Term-time	11 (68.8%)	5 (31.3%)
	School holidays	1 (6.3%)	3 (18.8%)
	Term and holiday	4 (25%)	8 (50%)
Recruitment source	Clinic	8 (50%)	-
	Charity	8 (50%)	-
	School	-	9 (56%)
	Online advertisement	-	6 (37.5%)
	Community groups	-	1 (6.3%)

4.2.2 Cognitive test results

Results from the cognitive assessment battery for the TS and control groups are displayed in Table 4. Independent samples t tests confirmed that the groups did not significantly differ on any of the measures administered.

4.2.3 Emotional and behavioural functioning scores

Questionnaire results for each group are displayed in Table 4. TS participants were rated as having significantly more symptoms of ADHD hyperactive-impulsive type than controls *[t(26)=3.26, p=.003]*. The TS group was also rated as having significantly more psychosocial difficulties *[SDQ self: t(26)=3.01, p=.006; SDQ parent: t(26)=2.76, p=.01]*, more symptoms of anxiety and depression *[RCADS self: t(12.83)=2.12, p=.054; RCADS parent: t(26)=3.24, p=.003]* and lower QoL *[PedsQL self: t(15.62)=-2.86, p=.011; PedsQL parent: t(26)=-2.45, p=.021]* than control participants. However, had Bonferroni corrections been performed on this data to control for multiple comparisons, the adjusted significance level would be .006. With this adjusted value, remaining significant differences between groups would be on the self-rated SDQ, parent-rated RCADS and Conner's hyperactive-impulsive scores.

Table 4 Neuropsychological battery and questionnaire scores by group

Domain	Measure	TS M(SD)	Control M(SD)	Statistics
IQ	2-subtest IQ (WASI)	105.07 (16.09)	109.19 (11.85)	t(30)= -0.82, p=.416
Processing speed	Cancellation (WISC-IV)	11.94 (2.23)	11.82 (3.12)	t(30)= 0.13, p=.897
Verbal working memory	Digit span (WISC-IV)	10.25 (3.47)	9.07 (2.86)	t(30)= 1.05, p=.300
Visuo-spatial working memory	Block recall (WMTB)	92.07 (16.31)	89.53 (11.85)	t(29)= 0.49, p=.627
Verbal learning and memory	CVLT-C short delay free recall	0.15 (1.10)	0.17 (0.79)	t(29)= -0.30, p=.976
	CVLT-C Long delay free recall	0.32 (1.02)	0.13 (1.06)	t(29)= 0.48, p=.634
Verbal inhibition	Colour-word interference: Inhibition	11.25 (2.01)	11.12 (1.96)	t(30)=0.18, p=.860
	Colour-word interference: Inhibition/switching	9.82 (3.08)	11.32 (2.42)	t(30)= -1.53, p=.136
Motor inhibition	Walk, don't walk (TEA-Ch)	7.75 (3.94)	7.69 (3.34)	t(30)= 0.48, p=.962
Visuo-motor co-ordination	Grooved pegboard: dominant hand	76.62 (10.38)	75.27 (13.95)	t(29)= 0.31, p=.760
	Grooved pegboard: non-dominant hand	85.57 (9.20)	81.47 (16.09)	t(29)= 0.88, p=.388
Phonological awareness	Blending words (CTOPP)	6.79 (3.50)	8.43 (3.26)	t(26)= -1.29, p=.209
Questionnaire	**Respondent**	**TS M, SD *(% in clinical range)***	**Control M, SD *(% in clinical range)***	**Statistics**
Strengths and Difficulties	Self	14.84, 6.63 ***(56.3%)***	8.53, 4.38 ***(6.3%)***	**t(26)= 3.01, p=.006****
Questionnaire (SDQ)-total	Parent	14.69, 6.88 ***(43.8%)***	8.33, 5.31 ***(18.8%)***	**t(26)= 2.76, p=.01***
Revised Children's Anxiety and	*Total anxiety and depression:* Self	49.90, 15.89 ***(43.8%)***	39.07, 6.96 ***(6.3%)***	t(12.83)= 2.12, p=.054
Depression Scale (RCADS)	Parent	60.84, 13.67 ***(50%)***	47.13, 8.46 ***(12.5%)***	**t(26)= 3.24, p=.003****
Paediatric Quality of Life	Self	69.72%, 17.73 ***(53.8%)***	85.84%, 9.14 ***(6.3%)***	**t(15.62)= -2.86, p=.011***
questionnaire (Peds-Ql)	Parent	61.92%, 21.63 ***(56.3%)***	78.40%, 13.49 ***(18.8%)***	**t(26)= -2.45, p=.021***
Conner's-3	*ADHD inattentive*	67.47, 17.91 ***(50%)***	55.87, 13.70 ***(18.8%)***	t(26)= 1.94, p=.064
	ADHD hyperactive/impulsive	76.31, 17.01 ***(81.3%)***	56.87, 14.56 ***(37.5%)***	**t(26)= 3.26, p=.003****

***** significant at p<.05 ** significant at p<.005

4.3 Main analysis

4.3.1 *Hypothesis 1: Children with TS will have more sleep difficulties than typically developing control participants.*

As Figure 2 shows, contrary to this hypothesis, there were no significant differences in sleep parameters between groups. This was confirmed with independent samples t-tests. Furthermore, Pearson's correlations showed no association between tic severity and sleep disturbance for the TS group. However, exploring the data further shows that TS participants had more variable sleep onset latency (SoL) than controls, reflected in the 95% confidence intervals displayed as error bars on Figure 2. The majority of TS scores fell between 18 and 71 minutes (range=53 minutes), while most controls took between 27 and 53 minutes to fall

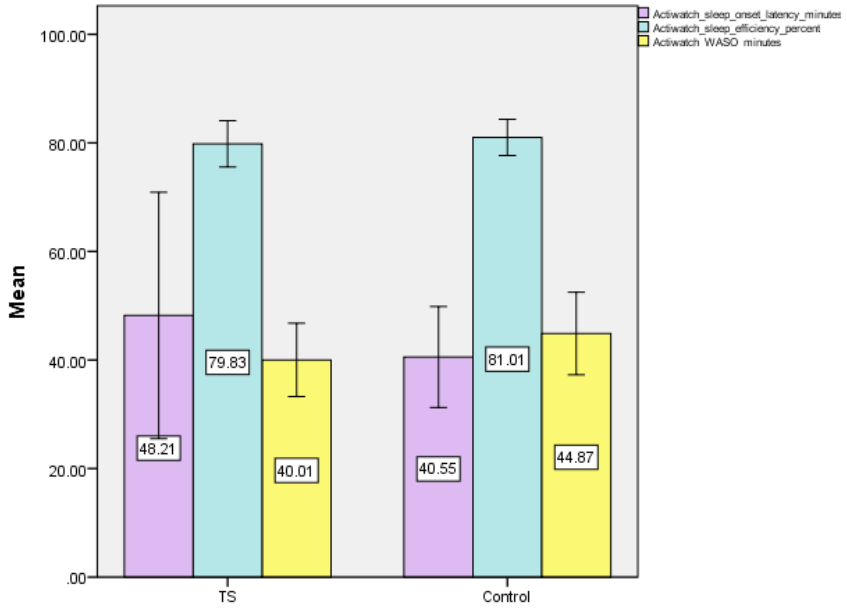

Figure 2 Actigraphy results by group

asleep (range=26 minutes).

WASO=wake after sleep onset

4.3.2 Hypothesis 2: Sleep difficulties will be associated with symptoms of psychological disorders in both groups, but this effect will be more pronounced in TS.

Pearson's correlations were conducted to explore relationships between sleep parameters and measures of emotional and behavioural functioning (see Appendix 13 for full results). The hypothesis was partially supported as in the TS group, SoL was found to be significantly associated with self-ratings of panic disorder symptoms [*RCADS self: r=.639, p=.034*] and parent rated depression [*RCADS parent: r=.630, p=.028*]. Sleep efficiency (SE) and wake after sleep onset (WASO) were not significantly associated with any of measures of emotional functioning in either group.

4.3.3 Hypothesis 3: Increased sleep disturbance will be associated with poorer performance on novel overnight cognitive learning tasks for both the TS and control groups. Whether this effect differs between groups will be explored.

4.3.3.1 Overnight change in performance

Before this hypothesis could be addressed, two-way repeated measures analyses of variance (ANOVA) were run to explore overall overnight change in performance between groups. These results are displayed in Table 5. No significant between-group differences were observed in performance change score (post-pre score) for any task. Trends in change scores are discussed below.

Table 5 Mean performance on Sleepsuite tasks pre- and post-sleep

Sleepsuite task		TS		Controls				
		Pre-sleep mean (SD)	*Post-sleep mean (SD)*	*Pre-sleep mean (SD)*	*Post-sleep mean (SD)*	*F(df)*	*p*	*d*
Animals (number correct)		7.85 (2.12)	7.31 (2.32)	6.80 (3.38)	6.27 (2.84)	.000 (1,26)	.995	.000
Mazes (time to target)		27.83 (15.66)	34.33 (26.97)	27.65 (15.56)	31.86 (24.76)	.134 (1,26)	.717	.005
Balloons (commission errors)	emotion	38.38 (33.42)	34.54 (26.91)	35.58 (29.72)	27.58 (24.44)	.240 (1, 23)	.628	.010
	gender	19.54 (22.94)	24.85 (14.12)	21.25 (12.88)	32.50 (23.93)	.349 (1, 23)	.561	.015

On the *Animals* task, neither group showed a clear performance change overnight. On the *Mazes* task both groups took longer to reach the target post- as compared to pre-sleep. For the *Balloons emotion* task performance in both groups improved overnight, more for controls than TS (controls=8 less errors; TS=4 less errors) although this difference was not significant *[F(1, 23)=.240, p=.628]*. On the *Balloons gender* task the opposite pattern was seen as both groups made more errors post-sleep (controls=11 more errors; TS=5 more errors) although this was not significantly different between groups *[F(1, 23)=.349, p=.561].*

4.3.3.2 Associations between SoL and Sleepsuite performance

The actigraphy variable used to represent sleep disturbance was SoL. This was expected to be the most sensitive measure of sleep difficulty in this sample because it was most different between groups and was the only sleep variable associated with psychopathology. The hypothesis was explored using a set of simple linear regressions and results are presented in Table 6.

Table 6 Associations between SoL and Sleepsuite task performance

Sleepsuite task		TS				Controls			
		B	*R*	R^2	*P*	*B*	*R*	R^2	*p*
Animals (number correct)		**-.026**	**.574**	**.329**	**.040***	.007	.058	.003	.851
Mazes (time to target)		.136	.364	.132	.222	.016	.019	.000	.950
Balloons (commission errors)	Emotion	-.079	.123	.015	.689	-.114	.057	.003	.867
	Gender	-.012	.019	.000	.951	-.481	.323	.104	.333

**=significant at p<.05*

On the A*nimals* task, longer SoL was significantly predictive of poorer performance for TS participants, explaining 33% of the variance in scores on this task *[R^2=.329, F(1, 11)=5.40, p=.04]*. For controls the effect was in the opposite direction but non-significant *[R^2=.003, F(1, 11)=.037, p=.851]*.

On the *Mazes* task, SoL was not significantly associated with performance for either group [TS: *R^2=.132, F(1, 11)=1.68, p=.222;* Controls: *R^2=.016, F(1, 11)=.004, p=.950]* but increased onset latency tended to be associated with worse performance post-sleep for both TS and control participants.

On the *Balloons emotion* task, SoL was not significantly associated with performance for either group. However in general, longer SoL was associated with less errors post- as compared to pre-sleep for TS [*R^2=.015, F(1, 11)=.169, p=.689*] and control groups [*R^2=.003, F(1, 9)=.030, p=.867*]. For the *Balloons gender* task, SoL was not significantly associated with performance for either group. Looking at the trend in the data, however, shows that longer SoL was associated with reduced errors post-sleep for both groups. This effect was stronger for controls [*R^2=.104, F(1, 9)=1.05, p=.333]* than for the TS group *[R^2=.000, F(1, 11)=.004, p=.951]*

4.4. Post-hoc analysis: Relationships between cognitive performance and sleep

Following the main analysis, it was of interest whether Sleepsuite performance would be associated with neuropsychological test scores differently for each group. Pearson's correlations were run to explore this and full results are presented in Appendix 14. Significant associations were observed for the TS group between processing speed and the *Animals task [r=.639, p=.019],* between reaction time and *Mazes task* performance *[r=.597, p=.03]* and between inhibition and B*alloons gender [r=-.626, p=.022].* No significant associations were observed between Sleepsuite performance and measures of cognitive functioning for the control group.

5 Discussion

5.1 Summary of aims and findings

This study builds on recent research (Modaferri et al., 2016; Weisner et al., 2017; Kirov et al., 2017) by exploring the functional impact of sleep difficulties and associations between sleep, wellbeing and learning in children with TS and healthy controls. Overall, no significant differences in sleep parameters were observed between groups although TS participants had more variable onset latency than controls. For the sample of children with TS, longer onset latency was also associated with significantly more psychosocial difficulties and poorer learning performance on a verbal memory task. No significant associations emerged between sleep, psychopathology and learning for control participants. Trends in the data are suggestive of different overnight learning profiles, which may be linked to different underlying cognitive mechanisms between groups.

5.1.1 Sleep in TS

Contrary to predictions, this study found no significant differences in sleep parameters between children with TS and healthy controls. Furthermore, no significant associations emerged between sleep parameters and parent-rated tic severity or tic-related impairment. Considered within the context of the already inconclusive evidence base for sleep problems in children with TS (Hibberd et al., 2017) the present findings do not support hypotheses that sleep disturbance is a central aspect of this disorder (Kirov et al., 2007) or that sleep and tics are directly linked. Instead, the findings of delayed sleep onset and a subsequent fairly efficient night of sleep for some children are more in line with suggestions that tics are ameliorated during sleep (Hashemiyoon et al., 2017). Despite the lack of significant differences in sleep between groups, TS participants did have more variable sleep than controls. This suggests that this group may be more at risk of disturbance than their typically developing peers, especially around sleep onset. It will therefore be important to consider factors which lead certain members of this potentially 'at risk' group to experience problematic sleep.

One previous suggestion is that sleep difficulties in TS are linked to medication use (Ayalon et al., 2002). Although this was not an exclusionary criteria for the present study, children were only able to participate following three months of pharmacological stability. This was felt by the expert authors (TH & PG) to be an adequate period for any adjustment-related medication effects (which may include sleep disturbance) to settle. It may therefore be that the sleep of children in the present sample was less affected by medications than in previous research (Hibberd et al., 2017) and could explain the lack of significant sleep disturbance found. More explicit explorations of this (i.e. directly comparing medicated to medication-

naïve children) in future studies will allow clearer conclusions to be drawn regarding the impact of medications on sleep in TS.

The lack of difference in sleep observed in the present study may also be at least partially due to aspects of the study itself. Most TS participants were monitored during term-time, while many of the controls were partly or solely monitored during holidays, a time when sleep tends to be less routine than normal (Danker-Hopfe, 2011). Participants' sleep-logs supported this, showing that during holidays many children had sleepovers and late evening social events, staying away from home and being permitted to wake later than during term-time. Although no statistically significant differences were observed in sleep parameters depending on time of participation, this nonetheless may have exerted some effect on the results and so should be controlled for in future.

Furthermore, as mentioned, this is the first study to have monitored sleep in children with TS using actigraphy as opposed to questionnaires or laboratory-based PSG methods. It may be that the particular types of sleep disturbance experienced by this group are not accurately detected by standard actigraphy. Indeed if children do tic overnight, it could be with less force than during the day or may occur in different parts of the body than the arm to which the actigraph is fastened (i.e. leg, facial or trunk tics; Galland et al., 2014). This could be further explored using overnight video-monitoring or multi-site accelometry where multiple actigraphs are fastened to different areas of the body (Galland et al., 2014). Although this would compromise some of the naturalistic benefits to actigraphy, and complicates a method which is attractive because of its simplicity, it would give richer information about whole-body motion during sleep. Additionally, a standardised sleep questionnaire was not administered to the present sample due to concerns that another measure may lead to participant fatigue and questionnaire non-compliance. However, without a subjective report qualitative aspects of sleep habits as well as family and child perceptions of sleep disturbance could not be explored. It will be helpful for future researchers to utilise mixed method paradigms (i.e. concurrent objective and subjective methods of sleep assessment) where possible to allow the most holistic understanding of the nature of sleep disturbance in this population to emerge (Gregory & Sadeh, 2016).

5.1.2 *Associations between sleep and functioning*

5.1.2.1 Psychopathology

Along with medication use another factor suggested to be related to sleep disturbance in children with TS is the presence of comorbid psychopathological conditions (Allen et al., 1992). In line with this, the most variable sleep parameter in the present study (sleep onset

latency; SoL) was significantly associated with symptoms of panic disorder and depression for TS participants but not for controls. While depression has previously been associated with sleep disturbance in this group (Modaferri et al., 2016), to our knowledge the relationship with panic has not been observed before. The TS-specific nature of these relationships suggests a particular mechanism linking these psychological disorders to sleep disturbance in this clinical group. Although the reasons for this are unclear, one possibility is that neuropathological changes underpinning both TS and comorbid disorders increase susceptibility to poor sleep. Indeed, neural changes across CSTC circuits as well as alterations to transmission of DA, 5-HT, GABA and glutamate have been observed in TS patients, as well as in those with depression and panic disorder (Mink, 2001; Santos, D'Amico & Dierssen, 2015; Peters et al., 2016). Importantly, these neural systems also facilitate sleep-wake regulation (Beebe, 2012). Although neurobiological changes are therefore likely to be one factor linking sleep, TS, depression and panic disorder, if the relationship were purely neurological associations would also be expected between TS, sleep and other conditions characterised by CSTC abnormalities (e.g. OCD; Ahmari, Spellman, Douglass, Kheirbek, Simpson, Deisseroth et al., 2013).

It may be that although the relationship involves neuropathological vulnerabilities, these only affect sleep within the context of particular psychological mechanisms. One candidate mechanism is adoption of a bias towards an internal focus of attention, or 'interoception'. Interoception has been found to be a common feature of TS (Pile, Lau, Topor, Hedderly & Robinson, 2017) and may be linked to tracking the premonitory urges which precede tics (Robinson & Hedderly, 2016). Similarly, in panic disorder catastrophic misinterpretations of bodily symptoms are thought to lead to a state of interoceptive hypervigilance (Yoris, Esteves, Couto, Melloni, Kichic, Cetkovich et al., 2015), while depressed patients show heightened interoception linked to a ruminative style of information processing (Shankman, Nelson, Sarapas, Robison-Andrew, Campbell, Altman, McGowan et al., 2013; Hamm, Richter & Panné-Farré, 2014; Northoff & Sibille, 2014; Paulus & Stein, 2010). The inherent threat appraisals associated with interoception in these disorders might cause feelings of anxiety, which could then activate the HPA axis and cause cortisol release, hyperactivity of which has previously been linked to sleep disturbance in TS (Buse et al., 2014; Corbett et al., 2008). It may therefore be that children with TS who are prone to interoception focus on internal sensations pre-sleep, possibly linked to concerns about tics occurring, causing physiological hyperarousal and subsequently delaying sleep onset. Although intriguing, this proposed mechanism is extremely tentative and necessitates further investigation in projects designed to understand more about pre-sleep cognitive processes in TS.

5.1.2.2 Learning

This was the first direct study of overnight consolidation in children with TS. Despite recent findings that TS patients and controls show opposing relationships between REM sleep duration and measures of neurobehavioural functioning (Kirov et al., 2017) it was unknown whether the specific process of consolidation would differ between these groups. It was also not known whether performance would be affected by aspects of the task or stimuli as in other neurodevelopmental disorders (e.g. reduced salience effect in ADHD; Weisner et al., 2017). Although effects were largely non- significant, exploring trends in the data uncovered opposing patterns of performance on the verbal learning A*nimals* task**.** While overall overnight performance change did not differ, SoL was significantly associated with performance for TS participants, with longer latency linking to worse performance; this effect was in the direction that would be expected. Unexpectedly however, the opposite effect was observed for controls, with longer SoL being linked to better performance following a night of sleep.

The reasons for this dissociation are unclear, however this task was the first to be administered post-sleep. With this in mind, it may be that typically developing populations show higher levels of inertia (post-wake disorientation following long sleep periods; Sadeh et al., 2002) than children with TS. In support of this, performance on cognitive tasks completed soon after wake is thought to be regulated by interactions between inertia, circadian rhythms and homeostatic processes (Burke, Scheer, Ronda, Czeisler & Wright, 2015). In clinical populations where these systems are affected (i.e. homeostasis in TS, Godar & Bortolato, 2016) the balance between these processes is likely to differ and this might then impact on task performance. In the present study both groups also took longer to complete the *Mazes* task of spatial learning following sleep, thus suggesting slower reaction times post-wake. This could be considered support for the impact of inertia on performance. Inertia may therefore affect cognition in a domain-specific manner, exerting a global effect across clinical and typically developing populations for certain skills (i.e. reaction speed) but differentially affecting others (i.e. verbally-mediated memory tests).

Group differences were also observed in the magnitude of changes on the continuous performance (*Balloons*) tasks. Although TS and controls showed effects in the same direction on both *Balloons* tasks, controls showed more of an improvement than TS on the *emotion* task, and more of a negative change on the *gender* task after sleep. This task was also more strongly associated with SoL for controls relative to TS participants. Unlike previous studies of children with ADHD (Weisner et al., 2017) there did not appear to be any particular effect of the salience of stimuli (i.e. emotion vs gender) within this task in children with TS and no significant association between performance and ADHD symptoms in this group. While this

could be suggestive of disorder-specific consolidation patterns across neurodevelopmental disorders, it may also reflect task-related or methodological differences between studies. To allow further clarification of the disorder-specificity of altered consolidation processes and rule out potential methodological confounds, future studies should aim to directly compare groups of children with different neurodevelopmental profiles and matched healthy control groups on the same consolidation task.

Following observation of different performance patterns on the A*nimals* task and magnitude of performance change on the *Balloons* tasks, it was wondered whether Sleepsuite performance might be underpinned by different cognitive skills between groups. This suggestion appeared to have some support. While no significant associations emerged between task performance and neuropsychological scores for controls, within the TS group significant associations were observed between processing speed, reaction time, inhibition and consolidation performance. This seems to suggest that children with TS rely more strongly on underlying cognitive skills to facilitate this process than their typically developing peers. Within the current actigraphy paradigm the neural mechanisms underpinning this could not be elucidated. However, extending the present findings to facilitate understanding of consolidation within the context of sleep stages will be a key task for future studies.

It is recognised that different types of information are consolidated during different sleep stages (e.g. SWS for episodic declarative memories and REM for emotional information; Walker, 2009; Weisner et al., 2015). This process has also been found to occur differently in ADHD and typically developing children (Prehn-Kristensen et al., 2011). Previous PSG studies have reached inconclusive results regarding sleep stage changes in children with TS, which is thought to be linked to methodological and sampling heterogeneity across studies (Hibberd et al., 2017). Thus, there is a need for larger-scale, more demographically varied and rigorously conducted projects that track associations between sleep stage distribution and processes of overnight consolidation in children with TS. These studies could also consider the 'sleep spindle' as another potential factor underpinning consolidation differences between clinical and non-clinical groups. This electroencephalographic event is generated by a thalamocortical neural network during stage two of sleep (Fogel & Smith, 2011) and is highly correlated with general cognitive abilities, processes of consolidation and learning efficiency (Hoedlmoser, Heib, Roell, Piegneux, Sadeh, Gruber & Schabus, 2014). Considering the characteristic thalamocortical changes in TS (Mink, 2001) and the different learning profiles observed in the present study, this may be another altered mechanism of consolidation in this clinical group.

5.2 Future research

Along with the ideas extending the current findings already proposed in this report, it would be useful to conduct more studies focusing on causes of sleep difficulties in TS. One way of doing this would be through conducting longitudinal studies tracking sleep in a single TS cohort over time. This would also allow more explicit testing of the theory proposed by Kirov et al (2014) that tics, sleep and neurobehavioural functioning are reciprocally related. Such studies could specifically look at factors which have been suggested to contribute to poor sleep in this group (e.g. physiological hyperarousal, Modafferi et al., 2016). This could be undertaken by testing markers of circadian regulation (e.g. cortisol levels) alongside sleep to see if these offer an explanation of sleep variability in TS (Honomichl et al., 2002).

Another interesting direction for future research would be to continue considering the functional implications of sleep difficulties in this group. One potential focus would be if, and how, sleep disturbance might translate into specific functional problems (i.e. with classroom learning or peer and social relationships) in TS. For instance, in ADHD attentional difficulties have been proposed to be amplified by sleep-dependent problems with memory and consolidation (Prehn-Kristensen et al., 2011). Although TS is not consistently associated with learning problems, and within the present sample no profile of cognitive impairment was observed, children with sleep disturbance within the context of TS may learn differently or show a different pattern of tic-related daytime symptoms to those who sleep well. For these studies it would be helpful to specifically recruit children with TS who report sleep disturbance as this would give more idea of the clinical characteristics and functional performance of this sample.

5.3 Strengths and limitations

This study has extended previous research into sleep in children with TS. It included a representative sample of TS participants recruited both from clinical and community settings and an age-, gender- and IQ-matched healthy control group. It controlled carefully for effects of adjustment to medication and thoroughly assessed other clinically relevant factors, including tic severity and psychopathology, using validated measures. It is the first study to have used actigraphy to explore sleep profiles in children with TS as well as drawing on research in other neurodevelopmental populations about possible daytime implications of sleep disturbance in this group. The findings offer initial insights into relationships between sleep and various functional domains in TS as well as into the process of overnight consolidation in this clinical group. It is hoped that these preliminary findings will be elaborated on in future projects.

Nonetheless, in line with the naturalistic and exploratory nature of this study, the findings should be interpreted cautiously. A key limitation of this project is the modest sample size. Furthermore, although age and gender were intentionally controlled for and the sample was designed to be clinically representative, it may not have been reflective of the most sleep-disturbed TS group. It has been suggested that sleep problems are most prevalent in TS around the age of 7 years (Sadeh et al., 2002) and that female patients may have more disturbed sleep than males (Storch et al., 2009). Additionally, because early adolescence is characterised by changes and maturation of sleep patterns (Barclay & Gregory, 2014), disturbances may be more likely at this developmental stage regardless of clinical status. Factors such as gender, age, ethnicity and socio-economic status have been acknowledged to impact on sleep and learning in typically developing populations (Sadeh et al., 2002). It would be helpful for future studies to recruit larger and more demographically diverse samples to allow the impact of these factors in TS to be more fully understood.

The method of consolidation assessment is another limitation of this study. The Sleepsuite tasks are novel and not yet validated, although this research is in progress. To the author's knowledge they have not previously been used in a naturalistic study (i.e. outside of the laboratory). One seemingly problematic consequence of this was that outside of the laboratory, children did not appear to always be compliant with the *Balloons* tasks, leading to several implausible results. This reduced the power of an already modest sample, rendering interpretations of the learning data tentative. It will be helpful to consider ways in future studies to further incentivise participation and help to increase participant effort on such tasks. It should also be highlighted that there was no significant difference in sleep between groups. It may therefore be that different conclusions regarding learning performance would be reached in the context of more problematic sleep.

5.4 Clinical implications

A key implication of the present findings is that sleep outcomes were not significantly different between samples of children with TS and healthy peers. This suggests that sleep difficulties are not an inevitable consequence of having TS as some children slept as well as, or better than, controls. Nonetheless, there was more evidence for variability in sleep in the TS group, suggesting that this group may be more 'at risk' of difficulties falling asleep than typically developing peers. This means that systematic screening of sleep should be an essential part of consultations with TS patients. Furthermore, sleep difficulties were related to symptoms of depression and panic disorder in TS children. This may mean that when sleep problems are highlighted, children could also be at risk of comorbid psychopathology, which should be explored further. Taking this integrated approach and considering sleep and

emotional functioning concurrently is in line with the notion that understanding sleep is central to understanding and enhancing wellbeing (Harvey et al., 2011; Maski & Kothare, 2013).

It is also hoped that when sleep and/or psychopathological difficulties have been screened for and identified they could be managed with targeted interventions. The most significant sleep disturbances in the present sample related to sleep onset, which were also specifically associated with psychopathology. The pre-sleep period may therefore be a key time at which interventions could be targeted. Indeed, Kirov et al (2014) have suggested that anxiety and subsequent cortisol release and muscle tension should be targeted within any intervention designed to improve sleep quality in TS. Simple behavioural and muscular relaxation strategies could therefore be routinely shared with children in clinical consultations. This may prevent or manage sleep onset problems early in their clinical course and thus minimise their functional impact.

5.5 Conclusions

This exploratory and novel study represents a first step towards characterising natural sleep patterns in a representative sample of children with TS. Sleep was highly variable in the clinical group but overall was not significantly different to the control group. This highlights the importance of screening these children for sleep difficulties especially around sleep onset, but suggests that sleep disturbance may not be a central aspect of TS. Children most at risk of poor sleep appeared to be those with TS and comorbid symptoms of psychological disorders (i.e. panic disorder, depression), which may be linked to interoceptive tendencies in this group. Tentative conclusions have been made regarding different patterns of learning and information consolidation in TS children compared to healthy controls, as well as around different associations between learning and cognition in this group. It is hoped that these initial suggestions will stimulate further research with the aim of improving detection and targeted management of sleep and associated difficulties in this patient group.

6.References

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7. Appendices

Appendix 1: Recruitment letter

We are writing to you with regard to participation in a research study being conducted as part of the Chief Investigator's Doctorate in Clinical Psychology. The project is investigating how quality of sleep might be linked with learning, behaviour and mood in children. We are particularly interested in exploring how these factors interact in young people with Tourette syndrome and Chronic Tic Disorders, compared to a similar group of students without these diagnoses. The findings of this study are anticipated to enhance our understanding of the relationship between sleep and learning during development, with the aim of informing future interventions

We are looking to recruit boys aged between 11 and 14 years to take part in the study. This includes both typically developing boys and boys with tic disorders.

The project involves wearing a particular type of watch, known as an actigraphy watch, during the day and at night for two weeks. The watch monitors the wearer's movement and this information will be used to learn about how well they are sleeping. To look at learning, the student will also be required to play some specially designed memory games on an iPad, one evening and then again the next morning. Both the watch and the iPad will be provided by our team. Participants will also be asked to complete some questionnaires and some standard tests to assess intellectual functioning and other cognitive skills. This one-off assessment is expected to take no more than two hours. Where possible, we are hoping to complete these assessments in a school setting.

To thank students for their participation, they will each receive a £10 Amazon voucher. We are unable to offer schools any financial incentive for assisting with participation, however, we hope you will be able to assist us with this project as it is an opportunity to be part of an exciting research project in a much needed area of study. Once the study is finished we will be able to send you a summary report of the study's findings, highlighting your schools invaluable involvement in the study.

We are very respectful of the pressures put upon students, and teachers alike, but hope that you will be able to help us with this project. If you have any queries, or would be interested in finding out more, please do not hesitate to contact us.

Yours sincerely,

Charlotte Hibberd
Trainee Clinical Psychologist and Chief Investigator
Addiction Sciences Building
Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark HillLondon, SE5 8AF
charlotte.hibberd@kcl.ac.uk

Appendix 2: Participant information sheets for NHS participants

Sheet A

Information sheet for participants aged 11-14

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

(*Version 4; 07/04/2016)*

We would like to ask you to take part in a postgraduate research study looking at sleep and learning in children with Tourette Syndrome or Chronic Tic Disorders. You should only take part if you want to and if you don't, that's absolutely fine - it will not affect you in any way! Before you decide if you want to take part, it is important you understand what is involved. Please read this sheet carefully, and talk to your parents about it. Ask if you would like some more information.

1. What is this about?

We would like to find out more about sleep in children with Tourette Syndrome or Chronic Tic Disorder, and if difficulties with sleep affect learning, mood and behaviour. People with Tourette Syndrome or Chronic Tic Disorder have 'tics', which are sudden repeated sounds or movements which can occur in any part of your body and can change over time. These findings will help us to help children with Tourette Syndrome or Chronic Tic Disorders with sleep problems. We will be comparing the results from this study to findings from children without Tourette syndrome and Chronic Tic Disorders.

2. Why are you asking me?

We are asking boys aged 11 to 14 with a diagnosis of Tourette Syndrome or Chronic Tic Disorder to take part in the study - it doesn't matter if you think you're a good or bad sleeper! If you don't want to take part, that's absolutely fine. And if you say yes, then decide you don't want to do it anymore, that's absolutely fine too. It's totally up to you. We will also ask your parent or carer whether they are happy for you to take part in the study.

3. What will happen if I say yes?

First, we will ask you and your parent/carer to come to Evelina Children's Hospital, or we will come to visit you at your home or school. This is so that you can answer some questions and do some different thinking puzzles, which most children say are quite fun!

We will then give you two things to take home.

1. A special watch that will look a bit like this

You will need to wear this watch in the day and at night for 2 weeks, so that it can collect information to tell us how you're sleeping. The watch is quite small so you will probably completely forget you're wearing it!

2. An iPad that has a special app with games on it.

We will ask you to take this home for a night and play the games one night before you go to bed, and then again when you wake up the next morning. We've heard from other children that these are pretty good fun!

The data from the study will be kept anonymously (so no-one will know that your results are yours) for up to 7 years.

4. What's good about doing this?

The study will help us learn about sleep in children with Tourette Syndrome and Chronic Tic Disorders, so we can offer other children who have these conditions better support and treatments. We also hope that the games and puzzles will be fun!

5. Could anything bad happen to me?

We don't think so. However, if you did feel upset or worried by anything, we will make sure there is someone for you to talk to about it. We will also be asking you some questions about your emotions (e.g. if you are a worrier or someone who gets sad about things). It's normal for everyone to feel worried or sad sometimes, but if we thought that you might feel more upset by things than others, we would want to try and make sure you have some help with this. To do this, we would first talk to you and your parents, we would then contact your GP (your everyday doctor) so that they could help too.

6. Who will know I've done this?

Your parents/carers, your GP (who is your everyday doctor), the doctors working in the TANDeM clinic at the Evelina Hospital and maybe also some of the teachers at your school will be the only people other than me who will know you've taken part. We won't tell any other doctors you might see.

7. How do I find out more?

If you want to know anything else after reading this sheet, you can speak to your parents/carers or contact me using the contact details:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

THANK YOU for readir
sheet and thinking abou

As another thank you f
the 2 weeks of the stu
£10 Amazon voucher!

Sheet B

INFORMATION SHEET FOR PARENTS OF PARTICIPANTS (*Version 4; 11/04/2016)*

REC Reference Number: **16/LO/0393**

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

This information sheet is for parents of participants with Tourette Syndrome/Chronic Tic Disorder

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

In this postgraduate research project, we are investigating how sleep might affect learning, behaviour and mood in children with Tourette Syndrome and Chronic Tic Disorders. This is important because we know that many children with Tourette Syndrome or Chronic Tic Disorders have problems getting to sleep, staying asleep, or do not have very good quality sleep. We also know that sleep is important for learning, and may also affect behaviour and mood. We would like to invite you and your child to be part of this study, but before you decide whether to take part, it is important that you understand why we are doing the study and what will be involved. Please remember that you do not have to take part in the study. Please take time to read this information carefully and discuss it with others if you wish. If anything is not clear, or you have any more questions after reading this, please ask.

1. **What are we trying to find out?**

We want to investigate (by monitoring your child's sleep, assessing thinking skills and completing questionnaires) how sleep affects learning, behaviour and mood in children with Tourette Syndrome/Chronic Tic Disorder. We will be comparing the results from this study to findings from children without Tourette syndrome and Chronic Tic Disorders. People diagnosed with Tourette Syndrome or Chronic Tic Disorder experience 'tics', which are sudden repeated movements or vocalisations. Tics can occur in any part of the body and often change over time. Some people have tics which are very obvious and noticeable, while in other people they can be much less visible. These findings will help us to help other children and young people with sleep problems with and without Tourette syndrome and Chronic Tic Disorders.

2. **Why has my child been asked to take part?**

We are asking boys aged 11 to 14 years who have a diagnosis of Tourette Syndrome/Chronic Tic Disorder and their parents to take part. As the study involves completing questionnaires, if you think that either you or your child will struggle to

understand and complete the questionnaires even with help (e.g. from you or the researcher) then we ask that you do not take part or let them take part.

If you decide that you and your child can take part, you are free to withdraw at any time without giving a reason. A decision not to take part, or to withdraw, will not affect you or your child in terms of healthcare or education. If you have any questions about this project and what you are being invited to take part in then please ask the researcher before you decide whether to participate. In addition to withdrawing you/your child from the study, you may also withdraw any data/information you/they have already provided up until 1st October 2016.

3. What will my child be asked to do?

You and your child will first be asked to complete some questionnaires about mood and general wellbeing, and your child will be asked to do some thinking puzzles, this will take about one to two hours and can either be done at the Evelina Children's Hospital, or at your child's school or your home, depending on what is easiest for you. Your child will then be asked to wear a special watch to monitor their sleep during the day and at night for 2 weeks. Before going to sleep on one of these nights and again when they wake up the next morning, we will ask your child to complete some puzzles on an iPad that we will provide. The games are designed for children, are meant to be fun, and take no more than 30 minutes to complete. Answers are completely private, and answers and scores will **not** be shared with anyone else.

4. Are there any benefits of taking part?

The study will have no direct benefit to you or your child, however the main benefit is being part of a study that will help us understand about sleep, learning and mood in young people with and without a diagnosis of Tourette Syndrome/Chronic Tic Disorder. This knowledge will help us develop targeted interventions for children with sleep problems. We will also be able to provide you and your child with information about sleep, learning and mood and where to seek support related to any of these areas, if needed.

5. Are there any risks?

The project does not have any likely risks associated with it. If your child does experience any distress related to the study at any point, there will always be someone available for them to talk to, or ask questions to. We will also routinely inform participants General Practitioners (GPs) of their involvement with the study so they will be aware of your child's participation should any difficulties arise.

Everything you and your child tell us is private and confidential. However, if either you or your child tells us something that means we are worried that there might be risk to you/them (e.g. that someone is hurting you/them) then we would need to break confidentiality. We would offer you/your child support and assist you/them to access appropriate help which will include writing to your GP for further assessment or support via a local Child and Adolescent Mental Health Service (CAMHS). If you are ever worried about yourself or your child then you can contact your GP for further advice.

6. **Will our participation be kept confidential? And how will our information be kept?**

To ensure confidentiality, your child will be randomly allocated a code. This unique code will be used on all questionnaires, measures and throughout data analysis so that no personally identifiable information will ever be associated directly with their data. If you and your child decide to take part, your consent form will be kept separately from their data and in a locked filing cabinet which only the main researchers will be able to access. Confidentiality will only be broken in the unlikely event that your child indicates potential harm to themselves or to others as it is the researcher's duty to pass on this information. In this case, the researcher would speak with you and possibly your GP, if necessary. Details will be kept for up to 7 years at King's College London, and then destroyed.

7. **What happens afterwards?**

The results of the study will increase our understanding of the relationship between sleep and learning in children and help us to develop interventions targeting difficulties in these areas. The results will also be submitted for publication but no personally identifiable information will be included in this. Please let the researcher know if you wish to receive a copy of the published article.

8. **What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [Charlotte Hibberd, charlotte.hibberd@kcl.ac.uk]. If you remain unhappy and wish to complain formally, you can do this through the Guy's and St Thomas' Patients Advice and Liaison Service (PALS) on 020 7188 8801, pals@gstt.nhs.uk. The PALS team are based in the main entrance on the ground floor at St Thomas' Hospital and on the ground floor at Guy's Hospital in the Tower Wing.

In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against Guy's and St Thomas' NHS Foundation Trust and/or King's College London but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

9. **How do I find out more?**

If you have any further questions after reading this sheet, you can contact me at any time:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

If this study has harmed you or your child in any way you can contact King's College London using the details below for further advice and information:

Charlotte Hibberd
charlotte.hibberd@kcl.ac.uk

Thank you for reading this information sheet and considering taking part.

As another thank you for taking part we will reimburse your family for your time with a £10 Amazon voucher.

Sheet C
INFORMATION SHEET FOR PARENTS OF PARTICIPANTS: (*Version 1; 12/04/2016)*

REC Reference Number: **16/LO/0393**

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

This information sheet is for parents of participants about their participation in the project

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

In this postgraduate research project, we are investigating how sleep might affect learning, behaviour and mood in children.

Please see the enclosed information sheet for further information about the background to the project, and what your child would be required to do if they decided to participate.

This extra information sheet aims to help you understand what would be required of you as a parent or guardian if your child takes part. Please remember that you and your child do not have to take part in the study. Please also take time to read this information carefully and discuss it with others if you wish. If anything is not clear, or you have any more questions after reading this, please ask Charlotte Hibberd using the contact details listed at the end of the page.

1. **What will I be asked to do?**

Your part in the study involves two main elements, completing a short diary of your child's sleep patterns for the two weeks they are in the study, and completing a set of questionnaires about their general mood and wellbeing. These elements will now be outlined in more detail.

1. The sleep diary is a short measure which asks you to note down the time your child goes to sleep and wakes up. It is important that you try to be as accurate as you can with this, although we do know it's sometimes hard to be totally exact! The diary also asks you to write down things like how many caffeinated drinks your child drinks in a day, and how much exercise they have done, which might affect how they're sleeping. These questions will help us to interpret the data from the watch your child would be wearing for the study. This measure is designed to be brief and hopefully should not take more than a few minutes to fill out each day.

2. Both you and your child will also be asked to complete some questionnaires. These include questions about your child's mood and general wellbeing, their behaviour and also about their symptoms of Tourette Syndrome/Chronic Tic Disorder. The questionnaires should not take a long time to complete and can either be done at the Evelina Children's Hospital (while you wait for your child to complete the 'thinking puzzle' part of the study, if you choose for them to do this at the hospital), or we can send them to you in the post to be completed at home. Charlotte Hibberd will be

contactable by email throughout your child's involvement with the study, and will be able to answer any further questions you might have about these questionnaires.

We will not be asking you any questions which are specifically about your own wellbeing, as all of the questionnaires will focus on your child's functioning.

Your answers will be kept completely private and confidential. However, if either you or your child tells us something that means we are worried that there might be risk to you/them (e.g. that someone is hurting you/them) then we would need to break confidentiality. We would offer you/your child support and assist you/them to access appropriate help. We will also be informing your GP of your child's involvement in the study, so that if you are at all worried about yourself or your child then you can contact your GP for further advice.

If you have any further questions after reading this sheet, or if you would like any more information about your involvement with it, you can contact me at any time:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

If this study has harmed you or your child in any way you can contact King's College London using the details below for further advice and information:

Charlotte Hibberd
charlotte.hibberd@kcl.ac.uk

Thank you for reading this information sheet and considering taking part.

Sheet D

Information sheet for participants with Tourette syndrome or Chronic Tic Disorder

We would like to ask you to take part in a postgraduate research study looking at sleep and learning in children with Tourette syndrome or Chronic Tic Disorders. You should only take part if you want to and if you don't, that's absolutely fine - it will not affect you in any way! Before you decide if you want to take part, it is important you understand what is involved. Please read this sheet carefully, and talk to your parents about it. Ask if you would like some more information.

1. What is this about?

We would like to find out more about sleep in children with Tourette syndrome or Chronic Tic Disorder, and if difficulties with sleep affect learning, mood and behaviour. These findings will help us to help children with Tourette syndrome or Chronic Tic Disorders with sleep problems. We will be comparing the results from this study to findings from children without Tourette syndrome and Chronic Tic Disorders.

2. Why are you asking me?

We are asking boys aged 11 to 14 with a diagnosis of Tourette syndrome or Chronic Tic Disorder to take part in the study - it doesn't matter if you think you're a good or bad sleeper! If you don't want to take part, that's absolutely fine. And if you say yes, then decide you don't want to do it anymore, that's absolutely fine too. It's totally up to you. We will also ask your parent or carer whether they are happy for you to take part in the study.

3. What will happen if I say yes?

First, we will come to visit you at your home or school. This is so that you can answer some questions and do some different thinking puzzles, which most children say are quite fun!

We will then give you two things to take home.

A special watch that will look a bit like this

You will need to wear this watch in the day and at night for 2 weeks, so that it can collect information to tell us how you're sleeping. The watch is quite small so you will probably completely forget you're wearing it!

An iPad that has a special app with games on it.
We will ask you to take this home for a night and play the games one night before you go to bed, and then again when you wake up the next morning. We've heard from other children that these are pretty good fun!

4. What's good about doing this?

The study will help us learn about sleep in children with Tourette syndrome and Chronic Tic Disorders, so we can offer children who have these problems better support and treatments. We also hope that the games and puzzles will be fun.

5. Could anything bad happen to me?

We don't think so. However, if you did feel upset or worried by anything, we will make sure there is someone for you to talk to about it.

6. Who will know I've done this?

Your parents/carers, the doctors working in the TANDeM clinic at the Evelina Hospital and maybe also some of the teachers at your school will be the only people other than me who will know you've taken part. We won't tell any other doctors you might see.

7. How do I find out more?

If you want to know anything else after reading this sheet, you can speak to your parents/carers or contact me using the contact details:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

THANK YOU for reading this info
thinking about taking part!

As a thank you for taking part, a
the study you will be given a £10

Sheet E
INFORMATION SHEET FOR PARENTS OF PARTICIPANTS

REC Reference Number: *HR15/162278*

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

This information sheet is for parents of participants with Tourette Syndrome/Chronic Tic Disorder

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

In this postgraduate research project, we are investigating how sleep might affect learning, behaviour and mood in children with Tourette Syndrome and Chronic Tic Disorders. This is important because we know that many children with Tourette Syndrome or Chronic Tic Disorders have problems getting to sleep, staying asleep, or do not have very good quality sleep. We also know that sleep is important for learning, and may also affect behaviour and mood. We would like to invite you and your child to be part of this study, but before you decide whether to take part, it is important that you understand why we are doing the study and what will be involved. Please remember that you do not have to take part in the study. Please take time to read this information carefully and discuss it with others if you wish. If anything is not clear, or you have any more questions after reading this, please ask.

1. **What are we trying to find out?**

We want to investigate (by monitoring your child's sleep, assessing thinking skills and completing questionnaires) how sleep affects learning, behaviour and mood in children with Tourette Syndrome/Chronic Tic Disorder. We will be comparing the results from this study to findings from children without Tourette syndrome and Chronic Tic Disorders. These findings will help us to help other children and young people with sleep problems with and without Tourette syndrome and Chronic Tic Disorders.

2. **Why has my child been asked to take part?**

We are asking boys aged 11 to 14 years who have a diagnosis of Tourette Syndrome/Chronic Tic Disorder and their parents to take part. As the study involves completing questionnaires, if you think that either you or your child will struggle to understand and complete the questionnaires even with help (e.g. from you or the researcher) then we ask that you do not take part or let them take part.

If you decide that you and your child can take part, you are free to withdraw at any time without giving a reason. A decision not to take part, or to withdraw, will not affect you or your child in terms of healthcare or education. If you have any questions about this project and what you are being invited to take part in then please ask the researcher before you decide whether to participate. In addition to withdrawing

you/your child from the study, you may also withdraw any data/information you/they have already provided up until 1st October 2016.

3. What will my child be asked to do?

You and your child will first be asked to complete some questionnaires about mood and general wellbeing, and your child will be asked to do some thinking puzzles, this will take about one to two hours and can either be done at your child's school or your home, depending on what is easiest for you. Your child will then be asked to wear a special watch to monitor their sleep during the day and at night for 2 weeks. Before going to sleep on one of these nights and again when they wake up the next morning, we will ask your child to complete some puzzles on an iPad that we will provide. The games are designed for children, are meant to be fun, and take no more than 30 minutes to complete. Answers are completely private, and answers and scores will **not** be shared with anyone else.

4. Are there any benefits of taking part?

The main benefit is being part of a study that will help us understand about sleep, learning and mood in young people with and without a diagnosis of Tourette Syndrome/Chronic Tic Disorder. This knowledge will help us develop targeted interventions for children with sleep problems. We will also be able to provide you and your child with information about sleep, learning and mood and where to seek support related to any of these areas, if needed. We will also reimburse your family for your time with a £10 Amazon voucher.

5. Are there any risks?

The project does not have any likely risks associated with it. If your child does experience any distress related to the study at any point, there will always be someone available for them to talk to, or ask questions to.

Everything you and your child tell us is private and confidential. However, if either you or your child tells us something that means we are worried that there might be risk to you/them (e.g. that someone is hurting you/them) then we would need to break confidentiality. We would offer you/your child support and assist you/them to access appropriate help. If you are ever worried about yourself or your child then you can contact your GP for further advice.

6. Will our participation be kept confidential? And how will our information be kept?

To ensure confidentiality, your child will be randomly allocated a code. This unique code will be used on all questionnaires, measures and throughout data analysis so that no personally identifiable information will ever be associated directly with their data. If you and your child decide to take part, your consent form will be kept separately from their data and in a locked filing cabinet which only the main researchers will be able to access. Confidentiality will only be broken in the unlikely event that your child indicates potential harm to themselves or to others as it is the researcher's duty to pass on this information. In this case, the researcher would speak with you and possibly your GP, if necessary. Details will be kept for up to 7 years at King's College London, and then destroyed.

7. What happens afterwards?

The results of the study will increase our understanding of the relationship between sleep and learning in children and help us to develop interventions targeting difficulties in these areas. The results will also be submitted for publication but no personally identifiable information will be included in this. Please let me know if you wish to receive a copy of the published article.

8. How do I find out more?

If you have any further questions after reading this sheet, you can contact me at any time:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

If this study has harmed you or your child in any way you can contact King's College London using the details below for further advice and information:

Professor Tony Charman
0207 848 5038
Tony.charman@kcl.ac.uk
charlotte.hibberd@kcl.ac.uk

Charlotte Hibberd

Thank you for reading this information sheet and considering taking part.

Sheet F

Information sheet for participants

We would like to ask you to take part in a postgraduate research study looking at sleep and learning. You should only take part if you want to and if you don't, that's absolutely fine-it will not affect you in any way! Before you decide if you want to take part, it is important you understand what is involved. Please read this sheet carefully, and talk to your parents about it. Ask if you would like some more information.

1. What is this about?

We would like to find out more about children's sleep, and if difficulties with sleep affect learning, mood and behaviour. These findings will help us to help children with sleep problems. We will be comparing the results from this study to findings from children with Tourette syndrome and Chronic Tic Disorders.

2. Why are you asking me?

We are asking boys aged 11 to 14 to take part in the study. It doesn't matter if you think you're a good or bad sleeper! If you don't want to take part, that's absolutely fine. And if you say yes, then decide you don't want to do it anymore, that's absolutely fine too. It's totally up to you.

We will also ask your parent or carer whether they are happy for you to take part in the study.

3. What will happen if I say yes?

First, we will come to your home or school so that you can answer some questions and do some different thinking puzzles, which most children say are quite fun! We will then give you two things to take home.

A special watch that will look a bit like this. You will need to wear this watch in the day and at night for 2 weeks, so that it can collect information to tell us how you're sleeping. The watch is quite small so you will probably completely forget you're wearing it!

An iPad that has a special app with games on it. We will ask you to take this home for a night and play the games one night before you go to bed, and then again when you wake up the next morning. We've heard from other children that these are pretty good fun!

4. What's good about doing this?

The study will help us learn about children's sleep, so we can offer children who have sleep problems better support and treatments. We also hope that playing the games and puzzles will be fun.

5. Could anything bad happen to me?

We don't think so. However, if you did feel upset or worried by anything, we'd make sure there is someone for you to talk to about it.

6. Who will know I've done this?

Your parents/carers, the doctors working in the TANDeM clinic at the Evelina Hospital and maybe also some of the teachers at your school will be the only people other than me who will know you've taken part. We won't tell any other doctors you might see.

7. How do I find out more?

If you want to know anything else after reading this sheet, you can speak to your parents/carers or contact me using the contact details:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

THANK YOU for reading this in
thinking about taking part!

As a thank you for taking part,
the study you will be given a £

Sheet G
INFORMATION SHEET FOR PARENTS OF PARTICIPANTS

REC Reference Number: *HR15/162278*

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

This information sheet is for parents of participants without Tourette Syndrome/Chronic Tic Disorder

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

In this postgraduate research project, we are investigating how sleep might affect learning, behaviour and mood in children. This is important because we know sleep problems are common in children. We also know that sleep is important for learning, and may affect behaviour and mood. We would like to invite you and your child to be part of this study, but before you decide whether you would like to take part, it is important that you understand why we are doing this study and what will be involved. Please remember that you do not have to take part in the study. Please take time to read this information carefully and discuss is with others if you wish. If anything is not clear, or you have any more questions after reading this, please ask.

1. **What are we trying to find out?**

We want to investigate (by monitoring your child's sleep, assessing thinking skills and completing questionnaires) how sleep affects learning, behaviour and mood in children. We will be comparing the results from this study to findings from children with Tourette syndrome and Chronic Tic Disorders. These findings will help us to help other children and young people with sleep problems with and without Tourette syndrome and Chronic Tic Disorders.

2. **Why has my child been asked to take part?**

We are asking boys aged 11 to 14 years (who do not have a diagnosis of Tourette Syndrome/Chronic Tic Disorder) and their parents to take part. As the study involves completing questionnaires, if you think that either you or your child will struggle to understand and complete the questionnaires even with help (e.g. from you or the researcher) then we ask that you do not take part or let them take part.

If you decide that you and your child can take part, you are free to withdraw at any time without giving a reason. A decision not to take part, or to withdraw, will not affect you or your child in terms of healthcare or education. If you have any questions about this project and what you are being invited to take part in then please ask the researcher before you decide whether to participate. In addition to withdrawing you/your child from the study, you may also withdraw any data/information you/they have already provided up until 1st October 2016.

3. **What will my child be asked to do?**

You and your child will first be asked to complete some questionnaires about mood and general wellbeing, and your child will be asked to do some thinking puzzles, this will take about one to two hours and can either be done at your child's school or your home, depending on what is easiest for you. Your child will then be asked to wear a special watch to monitor their sleep during the day and at night for 2 weeks. Before going to sleep on one of these nights and again when they wake up the next morning, we will ask your child to complete some puzzles on an iPad that we will provide. The games are designed for children, are meant to be fun, and take no more than 30 minutes to complete. Answers are completely private, and answers and scores will **not** be shared with anyone else.

4. **Are there any benefits of taking part?**

The study will have no direct benefit to you or your child. The main benefit is being part of a study that will help us understand about sleep, learning and mood in young people. This knowledge will help us develop targeted interventions for children with sleep problems. We will also be able to provide you and your child with information about sleep, learning and mood and where to seek support related to any of these areas, if needed. We will also reimburse your family for your time with a £10 Amazon voucher.

5. **Are there any risks?**

The project does not have any likely risks associated with it. If your child does experience any distress related to the study at any point, there will always be someone available for them to talk to, or ask questions to.

Everything you and your child tell us is private and confidential. However, if either you or your child tells us something that means we are worried that there might be risk to you/them (e.g. that someone is hurting you/them) then we would need to break confidentiality. We would offer you/your child support and assist you/them to access appropriate help. If you are ever worried about yourself or your child then you can contact your GP for further advice.

6. **Will our participation be kept confidential? And how will our information be kept?**

To ensure confidentiality, your child will be randomly allocated a code. This unique code will be used on all questionnaires, measures and throughout data analysis so that no personally identifiable information will ever be associated directly with their data. If you and your child decide to take part, your consent form will be kept separately from their data and in a locked filing cabinet which only the main researchers will be able to access. Confidentiality will only be broken in the unlikely event that your child indicates potential harm to themselves or to others as it is the researcher's duty to pass on this information. In this case, the researcher would speak with you and possibly your GP, if necessary. Details will be kept for up to 7 years at King's College London, and then destroyed.

7. What happens afterwards?

The results of the study will increase our understanding of the relationship between sleep and learning in children, and help us to develop interventions targeting difficulties in these areas. The results will also be submitted for publication but no personally identifiable information will be included in this. Please let the researcher know if you wish to receive a copy of the published article.

8. How do I find out more?

If you have any further questions after reading this sheet, you can contact me at any time:

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building, Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London
SE5 8AF
charlotte.hibberd@kcl.ac.uk

If this study has harmed you or your child in any way you can contact King's College London using the details below for further advice and information:

Professor Tony Charman
0207 848 5038
Tony.charman@kcl.ac.uk
charlotte.hibberd@kcl.ac.uk

Charlotte Hibberd

Thank you for reading this information sheet and considering taking part.

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES *(version 3; 07/04/2016)*

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

This consent form is for participants
'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

REC Reference Number: 16/LO/0393

Thank you for thinking about taking part in this research. If you have any questions, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to take home and keep.

Participant statement
I confirm that I understand that by ticking each box I am assenting to this part of the research. I understand that unticked boxes mean I DO NOT assent to that bit of the study. I understand that by not assenting to any one part, I might not be able to do the research at all.
Name:

Please tick

1. I have read the information sheet dated 07/04/2016 for the above study. I have been able to think about it and ask questions if I want to, which have been answered well-enough. ☐
2. I understand that it is up to me if I take part, and that even after it starts, I can decide to stop being in the study if I want to. ☐
3. I understand that no-one will be able to tell who I am from my scores or any information I've given to the researchers. ☐

Signature:

Date:

Researcher statement:

I confirm that I have carefully explained the nature and demands of this research study to the participant.

Name of researcher:

Signature:

Date:

CONSENT FORM FOR PARENTS OF PARTICIPANTS IN RESEARCH STUDIES *(version 2; 22/01/2016)*

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

This consent form is for <u>parents and carers</u>

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

REC Reference Number: 16/LO/0393

Thank you for considering taking part in this research. The person organising the research must explain the project to you and your child before you can agree to take part. If you have any questions arising from the information sheet, or discussions with the researcher or clinical team, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form for you to keep and refer to at any time.

Parent/guardian statement

I confirm that I understand that by ticking/initialling each box I am consenting that my family can participate in this element of the study. I understand that it will be assumed that unticked/initialled boxes mean that I DO NOT consent to my family taking part in that part of

Please tick/initial

1. I have read the information sheet dated 22/01/2016 for the above study and have talked to a member of the research or clinical team about it. I have had the opportunity to consider the information and ask questions, which have been answered satisfactorily. ☐

2. I understand that my family's participation is voluntary and that we are free to withdraw at any time, without giving reason, and without being affected in any way. Furthermore I understand that I will be able to request to withdraw the data until 1st October 2016. ☐

3. I consent to the processing of their personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998. ☐

4. I understand that my/my families data may be subject to review by responsible individuals from Guy's and St Thomas' NHS Foundation Trust and King's College London University. ☐

5. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify us in any publications. ☐

6. I agree to be contacted in the future by King's College London researchers who would like to invite me to take part in follow up studies to this project, or in future studies of a similar nature. ☐

the study. I understand that by not giving consent for any one element, my child may be deemed ineligible for the study.

Name of parent/guardian:

Signature:

Date:

Researcher statement:

I confirm that I have carefully explained the nature and demands of this research study to the participant.

Name of researcher:

Signature:

Date:

Appendix 5: Consent forms for non-NHS participants

CONSENT FORM FOR PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

This consent form is for participants

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

REC Reference Number: HR15/162278

Thank you for thinking about taking part in this research. If you have any questions, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form to take home and keep.

Participant statement
I confirm that I understand that by ticking each box I am agreeing to this part of the research. I understand that unticked boxes mean I DO NOT agree to that bit of the study. I understand that

Please tick

1. I have read the information sheet dated 18/12/2015 for the above study. I have been able to think about it and ask questions if I want to, which have been answered well-enough. ☐

by not agreeing to any one part, I might not be able to do the research at all.

2. I understand that it is up to me if I take part, and that even after it starts, I can decide to stop being in the study if I want to. ☐
3. I understand that no-one will be able to tell who I am from my scores or any information I've given to the researchers. ☐

Name:

Signature:

Date:

Researcher statement:

I confirm that I have carefully explained the nature and demands of this research study to the participant.

Name of researcher:

Signature:

Date:

CONSENT FORM FOR PARENTS OF PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.
This consent form is for <u>parents and carers</u>

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

REC Reference Number: HR15/162278

Thank you for considering taking part in this research. The person organising the research must explain the project to you and your child before you can agree to take part. If you have any questions arising from the information sheet, or discussions with the researcher or clinical team, please ask the researcher before you decide whether to join in. You will be given a copy of this consent form for you to keep and refer to at any time.

Parent/guardian statement

I confirm that I understand that by ticking/initialling each box I am consenting that my family can participate in this element of the study. I understand that it will be assumed that unticked/initialled boxes mean that I DO NOT consent to my family taking part in that part of the study. I understand that by not giving consent for any one element, my child may be deemed ineligible for the study.

Name of parent/guardian:

Please tick/initial

1. I have read the information sheet dated 18/12/2015 for the above study and have talked to a member of the research or clinical team about it. I have had the opportunity to consider the information and ask questions, which have been answered satisfactorily. ☐

2. I understand that my family's participation is voluntary and that we are free to withdraw at any time, without giving reason, and without being affected in any way. Furthermore I understand that I will be able to request to withdraw the data until 1st October 2016. ☐

3. I consent to the processing of their personal information for the purposes explained to me. I understand that such information will be handled in accordance with the terms of the UK Data Protection Act 1998. ☐

4. I understand that their information may be subject to review by responsible individuals from the college for monitoring and audit purposes. ☐

5. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify us in any publications. ☐

6. I agree to be contacted in the future by King's College London researchers who would like to invite me to take part in follow up studies to this project, or in future studies of a similar nature. ☐

Signature:

Date:

Researcher statement:

I confirm that I have carefully explained the nature and demands of this research study to the participant.

Name of researcher:

Signature:

Date:

Appendix 6: GP letter for NHS participants

Tics and NeuroDevelopmental Movements
Children's Neurosciences Centre
Floor 1 (Lift/ Stairs D), South wing
St Thomas' Hospital
Westminster Bridge Road
London SE1 7EH

Department: 020 7188 4661
Fax: 020 7188 4629
Main Switchboard: 020 7188 7188

'A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders'

This letter is for information only and no action is required. It is to inform you that your patient _____ is participating in a research project being conducted by researchers at King's College London and Evelina London Children's Hospital. The project is investigating how quality of sleep might be linked with learning, behaviour and mood in children with and without tic disorders. The findings of this study are anticipated to enhance our understanding of the relationship between sleep and learning during development, with the aim of informing future interventions.

The project involves the participant wearing an actigraphy watch for two weeks to monitor movement and provide information about sleep quality. To look at learning, participants will be play specially designed memory games on an iPad, one evening and then again the next morning. Participants will also be asked to complete standard tests of intellectual functioning and other cognitive skills, as well as questionnaires about emotional and behavioural functioning.

The study is not expected to have any adverse effects for participants. However, should your patient disclose any information that makes the research team concerned for their safety, or the safety of those around them, we will contact yourselves in the interests of safeguarding.

If you require any more information please do not hesitate to contact me using the details below.

Yours sincerely,

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building
Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London, SE5 8AF
charlotte.hibberd@kcl.ac.uk

Appendix 7: Ethical approval letter from KCL REC

Research Ethics Office

Franklin Wilkins Building
5.9 Waterloo Bridge Wing
Waterloo Road
London SE1 9NH
Telephone 020 7848 4020/4070/4077
rec@kcl.ac.uk

KING'S College LONDON

Charlotte Hibberd

23 December 2015

Dear Charlotte,

Study Title: A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders

Study Reference: HR-15/16-2278

I am pleased to inform you that full approval for your project has been granted by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee

Please ensure that you follow all relevant guidance as laid out in the King's College London Guidelines on Good Practice in Academic Research (http://www.kcl.ac.uk/college/policyzone/index.php?id=247).

For your information, ethical approval is granted until 23rd December 2018. If you need approval beyond this point, you will need to apply for an extension at least two weeks before this. You will be required to explain the reasons for the extension. However, you will not need to submit a full re-application unless the protocol has changed. If you have been granted approval for only 12 months, you will not be sent a reminder when it is due to lapse.

Ethical approval is required to cover the data-collection phase of the study. This will be until the date specified in this letter. However, you do not need ethical approval to cover subsequent data analysis or publication of the results.

For secondary data-analysis, ethical approval is applicable to the data that is sensitive or identifies participants.

Approval is applicable to period in which such data is accessed or evaluated.

Please note you are required to adhere to all research data/records management and storage procedures agreed to as part of your application. This will be expected even after the completion of the study.

If you do not start the project within three months of this letter, please contact the Research Ethics Office.

Please note that you will be required to obtain approval to modify the study. This also encompasses extensions to periods of approval. Please refer to the URL below for further guidance about the process:

http://www.kcl.ac.uk/innovation/research/support/ethics/applications/modifications.aspx

Please would you also note that we may, for the purposes of audit, contact you from time to time to ascertain the status of your research.

If you have any query about any aspect of this ethical approval, please contact the Research Ethics Office: (http://www.kcl.ac.uk/innovation/research/support/ethics/contact.aspx)

We wish you every success with this work.

Yours sincerely,

James Patterson - Senior Research Ethics Officer

For and on behalf of

Professor Gareth Barker, Chair of the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee

Cc: Tony Charman

Appendix 8: Ethical approval letter from NHS REC

NHS
Health Research Authority

London - Camden & Kings Cross Research Ethics Committee
Room 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne & Wear

NE32 3DT

Telephone: 0207 104 8087

16 May 2016

Dr Sally Robinson
Children's Neurosciences Centre, Floor 1 Staircase D South Wing
St Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH

Dear Dr Robinson

Study title:	**A naturalistic study investigating sleep and cognitive learning in children with and without tic disorders**
REC reference:	**16/LO/0393**
IRAS project ID:	**191384**

Thank you for your letter of 03 May 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.
The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.
We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Christie Ord at nrescommittee.london-camdenandkingscross@nhs.net.

Confirmation of ethical opinion
On behalf of the Committee, I am pleased to confirm a **favourable** ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.
Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ('Participant Identification Centre'), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).
There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.
To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.
If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made.
Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see 'Conditions of the favourable opinion' above).
Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP_letter]	1	05 April 2016
Letters of invitation to participant [Letter_to_schools]	1	20 November 2015
Non-validated questionnaire [Sleep_diary]	1	19 November 2015
Other [PG_brief_CV]	1	19 February 2016
Other [TH_brief_CV]	1	19 February 2016
Other [Information_letter_schools]	1	05 April 2016
Participant consent form [Consent_form_parents]	2	22 January 2016
Participant consent form [Consent_form_YP]	2	22 January 2016
Participant consent form [Actiwatch_consent]	1	19 November 2015

Participant consent form [Consent_form_YP]	3	07 April 2016
Participant information sheet (PIS) [Actiwatch_information_sheet]	1	19 November 2015
Participant information sheet (PIS) [Information_sheet_parents_control]	4	11 April 2016
Participant information sheet (PIS) [Information_sheet_parents_TS]	4	11 April 2016
Participant information sheet (PIS) [Parent_information_sheet]	1	12 April 2016
Participant information sheet (PIS) [Information_sheet_YP_control]	4	07 April 2016
Participant information sheet (PIS) [Information_sheet_YP_TS]	4	07 April 2016
REC Application Form [REC_Form_24022016]		24 February 2016
Referee's report or other scientific critique report [Reviewer_report]	1	18 October 2015
Research protocol or project proposal [Protocol]	3	22 January 2016
Summary CV for Chief Investigator (CI) [SR_CV]	1	29 January 2016
Summary CV for student [CH_brief_CV]	1	19 February 2016
Summary CV for supervisor (student research) [TC_brief_CV]	1	19 February 2016
Validated questionnaire [Conners 3]		
Validated questionnaire [GTS-QoL]		
Validated questionnaire [MOVES]		
Validated questionnaire [PedsQL_parent_8-12]		
Validated questionnaire [PedsQL_parent_13-18]		
Validated questionnaire [PedsQL_YP_8-12]		
Validated questionnaire [PedsQL_YP_13-18]		
Validated questionnaire [RCADS_parent]		
Validated questionnaire [RCADS_self]		
Validated questionnaire [SDQ_parent]		
Validated questionnaire [SDQ_self]		
Validated questionnaire [YGTSS]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *'After ethical review – guidance for researchers'* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/LO/0393 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely pp

Mrs Eleni Yerolaki Alternate Vice-Chair

Email:nrescommittee.london-camdenandkingscross@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

'After ethical review – guidance for Researchers' *[SL-AR2]*

Copy to: *Elizabeth Bruna, Guy's and St Thomas' NHS Foundation Trust Jennifer Boston, Guy's and St Thomas' NHS Foundation Trust*

London - Camden & Kings Cross Research Ethics Committee

Attendance at Sub-Committee of the REC meeting held in correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms Petra Shroff	Paediatric Nurse	Yes	
Ms Eleni Yerolaki	Specialist Counsellor	Yes	Alternate Vice-Chair

Also in attendance:

Name	*Position (or reason for attending)*
Miss Kirstie Penman	REC Assistant

Appendix 9: Actiwatch information sheet, consent form and sleep diary

ACTIWATCH INSTRUCTIONS

The actiwatch you have been given is a device that monitors activity, both day and night. It should be worn like a watch continuously for the desired duration. **It should only be removed if it is likely to get wet** for example in the bath or when swimming.

To ensure the actiwatch is attached correctly, please secure it to your child's non dominant wrist (i.e. on their non-writing side).

It will be "active" for the whole time and cannot be accidentally switched off. It is very important that it is put on as soon as it is received.

To help get as much information as possible **please complete the enclosed sleep log** with as much detail as possible, including the start date and times of "lights out"/settling time.

You should return the watch at the end of the two week monitoring period in line with the agreement you have made with the study team. This will either be via their school, by Special Delivery post, or will be collected from you by one of the research team.

If you experience any problems or have any queries or concerns related to this study, please let us know by telephone or email as soon as possible.

Many thanks,

Charlotte Hibberd
Trainee Clinical Psychologist
Addiction Sciences Building
Institute of Psychiatry, Psychology and Neuroscience (IoPPN)
4 Windsor Walk, Denmark Hill
London, SE5 8AF
charlotte.hibberd@kcl.ac.uk

enclosed:
Actiwatch with strap
Sleep Log for home
Letter for School

AMBULATORY SLEEP MONITORING: ACTIWATCH

Participant number:	
DOB:	
Type of Actiwatch and S/N:	

Please read the following carefully before giving your consent. If you feel you are unable to abide by the terms and conditions of this loan you will not be issued this device and alternative arrangements will be necessary.

1. The equipment is loaned to me and remains the property of the Guy's and St Thomas' NHS Foundation Trust, Evelina Children's Hospital London at all times.
2. I must take care of the equipment loaned to me. I will be responsible for replacement costs should any loss occur.
3. I must return the equipment on the date indicated below. Failure to return the equipment promptly results in a delay in the study.

Issue Date:	Return Date:

RETURN OF EQUIPMENT:

The device must be returned at the end of your child's study in line with the agreement you have made with the researchers. This will either be to their school, by Special Delivery post, or will be collected from you by one of the research team. Should you accidently lose or damage the watch it is important that you contact Charlotte Hibberd as soon as possible by emailing charlotte.hibberd@kcl.ac.uk.

Please sign the below to indicate that you understand the conditions of the loan:

Print name ……..

Signed ……..

Print name ……..

Signed ……

To whom it may concern

The owner of this letter is undergoing a research study and is wearing an actiwatch on their wrist. The purpose of the study is to discover more about the wearer's sleep patterns by measuring day and night time activity for two weeks.

The device does not make any noise and cannot be switched off accidentally. The only important thing to remember is that it's not waterproof and needs to be removed before showers or swimming, kept in a safe place and put back on as soon as possible. It would be very useful if a note of any time the watch is removed can be made and handed back to the child or their parents at the end of the study.

If you require more information please email me using the details below.

Yours sincerely

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Actigraphy Sleep Log

Participant number:	**Start Date and Time**

During the actigraphy study it will help us to interpret the results correctly if you and your child can complete the sleep and activity log below. It's important to be as accurate as you can with the times. Please contact us with any queries, thank you.

	Example	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date	Mon 05/08							
Daytime naps, times and length	5.30pm 20mins							
Medications Type, amount and time taken	Clonidine 8am 25mcg							
Cola, tea, coffee. Time and amount (any caffeinated	8am tea x2 6pm cola x1							
Actiwatch removed, time, duration and reason	6.45am 20mins shower							
Time spent in bed before lights out, type of activity	15mins reading							
LIGHTS OUT	10pm							
Sleep start time	10.30pm							
Awakenings, Time and duration	12am 20mins 2am 30mins							
Final awakening time	6.30am							

If the day was unusual or may have an effect on your child's normal sleep pattern then please let us know below e.g. T=term time/H=Holidays

Day 1_____

Day 2_____

Day 3_____

Day 4_____

Day 5_____

Day 6_____

Day 7_____

	Example	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date	Mon 05/08							
Daytime naps, times and length	5.30pm 20mins							
Medications Type, amount and time taken	Clonidine 8am 25mcg							
Cola, tea, coffee. Time and amount (any caffeinated	8am tea x2 6pm cola x1							

Actiwatch removed, time, duration and reason	6.45am 20mins shower							
Time spent in bed before lights out, type of activity	15mins reading							
LIGHTS OUT	10pm							
Sleep start time	10.30pm							
Awakenings, Time and duration	12am 20mins 2am 30mins							
Final awakening time	6.30am							

If the day was unusual or may have an effect on your normal sleep pattern then please let us know below e.g. T=term time/H=Holidays

Day 8_____

Day 9_____

Day 10_____

Day 11_____

Day 12_____

Day 13_____

Day 14_____

Any additional comments:

Appendix 10: Full descriptions of Neuropsychological measures

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2011)

The WASI-II (Wechsler, 2011) is a brief measure of general intellectual functioning which is comprised of 4 subtests, Block Design (BD), Vocabulary (Vc), Matrix Reasoning (MR) and Similarities (Si). The WASI-II gives a range of index scores representing the participants' crystallised abilities, in the verbal comprehension (VCI) score, their non-verbal abilities, in the perceptual reasoning index (PRI) and an overall, measure of general cognitive ability, the full-scale IQ (FSIQ). The WASI-II offers flexible administration options, comprising the measure of overall intelligence either from all 4, or from 2 subtests (Vc & MR). For this project, the subtests comprising the 2-subtest FSIQ were completed as a minimum. Subtests are scored using scaled scores, ranging from 1-20, with an average of 10. Indices give standard scores, which are scored from <60 to >

Digit Span (WISC-IV subtest; Wechsler, 2003)

This measure of verbal working memory is taken from the Wechsler Intelligence Scale for Children fourth edition (WISC-IV; Wechsler, 2003). It is comprised of two trials, digits forward and digits backwards. For the former, children are required to repeat a string of between 3-9 digits, while the latter requires manipulation of number strings from 2-9, which must be repeated in reverse order (i.e. 'backwards'). The subtest is scored from 1-20, with an average of 10.

Cancellation (WISC-IV subtest; Wechsler, 2003)

The cancellation subtest, taken from the Wechsler Intelligence Scale for Children fourth edition (WISC-IV; Wechsler, 2003) is a measure of processing speed. Participants have 45 seconds to mark selected targets (i.e. all the animals they can see among an array of target and distractor stimuli) on a random, and then a structured array. The subtest is scored from 1-20, with an average of 10.

Block Recall (Working Memory Test Battery subtest; Gathercole & Pickering, 2001)

Block Recall is a span task, taken from the Working Memory Test Battery (WMTB; Gathercole & Pickering, 2001), and is designed to assess visuo-spatial working memory. The stimuli consist of a board with nine raised blocks in what appears to the child as a "random" arrangement. The blocks have numbers on one side that can only be seen from the experimenter's perspective. The experimenter taps a block (or series of blocks), and the child's task is to duplicate the tapping in the same order as presented by the experimenter.

California Verbal Learning Test for Children (CVLT-C; Delis et al., 1994)

The *CVLT-C* (Delis et al., 1994) assesses verbal learning through an everyday memory task in which the child is asked to recall a list of nouns in the form of a shopping list. An interference task is given, followed by short-delay free recall and cued recall trials. Free recall, cued recall and a word recognition trial are also administered after a 20-minute delay. Raw scores for the task are converted into age-defined standard scores, with an increment of 0.5, ranging from -5 to +5, with an average of 0.

Colour-word interference (DKEFS; Delis et al., 2001)

The Color-Word Interference Test (CWIT) from Delis-Kaplan Executive Functioning System (DKEFS; Delis et al., 2001), which consists of four parts: Color naming, word reading, inhibition, and inhibition/switching. The CWIT begins with the color naming trial, in which people are

presented with a page containing a series of red, green, and blue squares, and are asked to say the names of the colors as quickly as he/she can without making mistakes. The word reading trial is second, in which people are presented with a page containing the words “red,” “green,” and “blue” printed in black ink. People are asked to read the words aloud as quickly as he/she can without making mistakes. The inhibition (i.e. stroop task) trial is third, in which the patient is presented with a page containing the words “red,” “green,” and “blue” printed incongruently in red, green, or blue ink. People are asked to say the color of the ink in which each word is printed as quickly as he/she can without making mistakes. Last is the inhibition/switching trial, in which people are presented with a page containing the words “red,” “green,” and “blue” written in red, green, or blue ink. Half of these words are enclosed within boxes. People are asked to say the color of the ink in which each word is printed (as in the third trial), but to read the word aloud (and not name the ink color) when a word appears inside a box, as quickly as he/she can without making mistakes. Performance is measured by completion time on each of the four trials, for which raw scores are converted into age-defined scaled scores, ranging from 1-19.

Walk, don’t walk (TEA-Ch subtest; Manly et al., 1998)

This subtest from the Test of Everyday Attention for Children (TEA-Ch; Manly et al., 1998) assesses sustained attention and response inhibition. Children are asked to take one ‘step’ with a pen along a paper path, after each tone they hear on a tape. Unpredictably one tone ends differently than the rest, signaling the child to stop. The test measures whether or not the child is able to stop responding when the signal occurs or is `carried away' into a task driven `automatic' style of responding, and/or unable to inhibit this response. Raw scores for correct responses are converted into age- and gender-defined scaled scores ranging from 1-19.

Grooved Pegboard Test (Klove, 1963)

This manipulative dexterity test contains twenty-five holes with randomly positioned slots and pegs which have a key along one side. Pegs must be rotated to match the hole before they can be inserted, and should be filled as soon as possible, without skipping any slots. Only one peg can be picked up at a time, and only one hand must be used. The dominant hand is tested first, and the test is scored by time taken to place all the pegs.

Blending Words (CTOPP subtest; Wagner et al., 2013)

This measure of phonological awareness, taken from the Comprehensive Test of Phonological Processing, second edition (CTOPP-2). A tape is played featuring words broken down into individual sounds (‘phonemes’). People must blend the phonemes and correctly identify the word. The test is scored based on number of items correctly identified, with raw scores converted into standardised scaled scores, ranging from 1-20.

Appendix 11: Full descriptions of questionnaire battery

Conners 3rd edition (Conners-3; Conners, 2008)

The Conners-3 is a parent-report assessment of behaviour and ADHD symptoms. It provides evaluation of the key areas of inattention, hyperactivity/impulsivity, learning problems, executive functioning, aggression, and peer relations. It is scored using age- and gender-defined T scores.

Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997)

The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioural screening questionnaire about 3-16 year olds. It includes 25 items on psychological attributes, divided between 5 scales (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems & prosocial behaviour), and an impact supplement (which asks whether the respondent thinks the young person has a problem, and if so, enquire further about chronicity, distress, social impairment, and burden to others).

Revised Children's Anxiety and Depression Scale (RCADS; Chorpita et al., 2001)

The Revised Child Anxiety and Depression Scale (RCADS) is a 47-item, youth self-report questionnaire with subscales including separation anxiety disorder (SAD), social phobia (SP), generalized anxiety disorder (GAD), panic disorder (PD), obsessive compulsive disorder (OCD), and major depressive disorder (MDD). It also yields a Total Anxiety Scale (sum of the 5 anxiety subscales) and a Total Internalizing Scale (sum of all 6 subscales). Items are rated on a 4-point Likert-scale from 0 ("never") to 3 ("always"). Additionally, The Revised Child Anxiety and Depression Scale – Parent Version (RCADS-P) similarly assesses parent report of youth's symptoms of anxiety and depression across the same six subscales.

Paediatric Quality of Life (PedsOL; Varni et al., 1999)

This self- and parent- report measure which asks about a young person's physical, emotional, social and school functioning, with presence of problems rated on a 5-point Likert-scale from 0 ("never") to 4 ("almost always"). It is scored by reverse scoring and then linearly transforming each item onto a 0-100 scale, giving a percentage representing the young person's quality of life, with higher scores indicating a better quality of life.

Appendix 12: YGTSS scores for overall sample and group by recruitment source

		TS overall (N=16) Mean (SD, Range)	**TS clinic** (N=8) Mean (SD, Range)	**TS charity** (N=8) Mean (SD, Range)	**Statistics**
Number of tics (max=5)	Motor	3.40 (0.98, 2-5)	3.29 (1.26, 2-5)	3.50 (0.75, 2-4)	t(9.59)= -3.94, p=.702
	Phonic	2 (1, 0-3)	1.71 (0.96, 0-3)	2.25 (1.03, 0-3)	t(13)= -1.04, p=.318
Frequency of tics (max=5)	Motor	3.73 (1.03, 1-5)	3.15 (1.06, 1-4)	4.25 (0.70, 3-5)	**t(13)= -2.40, p=.032***
	Phonic	3 (1.52, 0-5)	2.29 (1.11, 0-3)	3.62 (1.60, 0-5)	t(13)= -1.86, p=.086
Overall tic severity score (max=50)		26.20 (8.21, 6-42)	24.85 (10.77, 6-42)	27.37 (5.69, 18-34)	t(13)= -.578, p=.573
Tic severity + impairment (max=100)		50.20 (15.82, 6-82)	47.71 (22.75, 6-82)	52.37 (6.71, 42-64)	t(13)= -.555, p-.588

**=significant at p<.05;*

Number ratings: *0 (none), 1 (single tic), 2 (2-5 discrete tics), 3 (5 discrete tics), 4 (multiple discrete and at least one orchestrated pattern/sequence of tics), 5 (multiple discrete and multiple orchestrated patterns/sequences of tics).*

Frequency ratings: *0 (none), 1 (rarely present), 2 (occasionally present), 3 (frequently present), 4 (almost always present), 5 (always present).*

Appendix 13: Association between sleep variables and questionnaire scores by group

TS group				
Measure	Rater	Sleep onset latency (mins)	Sleep efficiency (%)	Wake after sleep onset (mins)
SDQ: Total difficulties	Self	r=.333, p=.266	r=-.220, p=.470	r=-.088, p=.776
	Parent	**r=.577, p=.050***	r=-.454, p=.138	r=-.109, p=.736
RCADS: Separation anxiety	Self	r=.600, p=.051	r=-.585, p=.059	r=-.202, p=.551
	Parent	r=.558, p=.060	r=-.417, p=.178	r=-.292, p=.356
RCADS: Generalised anxiety	Self	r=.464, p=.150	r=-.439, p=.177	r=-.280, p=.405
	Parent	r=.541, p=.069	r=-.431, p=.162	r=-.145, p=.652
RCADS: Panic disorder	Self	**r=.639, p=.034***	r=-.580, p=.061	r=-.091, p=.791
	Parent	r=.461, p=.131	r=-.265, p=.406	r=-.288, p=.363
RCADS: Social phobia	Self	r=.425, p=.192	r=-.481, p=.134	r-.090, p=.793
	Parent	r=.466, p=.127	r=-.500, p=.098	r=.139, p=.666
RCADS: OCD	Self	r=.546, p=.082	r=-.316, p=.344	r=-.578, p=.063
	Parent	r=.385, p=.216	r=-.154, p=.633	r=-.512, p=.089
RCADS: Depression	Self	r=.473, p=.142	r=-.521, p=.100	r=.236, p=.485
	Parent	**r=.630, p=.028***	r=-.524, p=.080	r=-.019, p=.953
Conner's: Inattentive	Parent	r=.425, p=.168	r=-.302, p=.341	r=-.211, p=.510
Conner's: Hyperactive impulsive	Parent	r=.356, p=.256	r=-.233, p=.467	r=-.081, p=.803
Control group				
		Sleep onset latency (mins)	Sleep efficiency (%)	Wake after sleep onset (mins)
SDQ: Total difficulties	Self	r=.070, p=.830	r=-.129, p=.690	r=.072, p=.824
	Parent	r=-.527, p=.078	r-.379, p=.224	r=-.018, p=.956
RCADS: Separation anxiety	Self	r=-.151, p=.638	r=-.049, p=.880	r=.072, p=.824
	Parent	r=-.044, p=.891	r=-.009, p=.979	r=-.178, p=.580
RCADS: Generalised anxiety	Self	r=-.473, p=.120	r=.548, p=.065	r=-.389, p=.211
	Parent	r=-.365, p=.243	r=.441, p=.152	r=-.376, p=.228
RCADS: Panic disorder	Self	r=-.186, p=.603	r=-.080, p=.806	r=.269, p=.398
	Parent	r=.240, p=.453	r=-.509, p=.091	r=.430, p=.163
RCADS: Social phobia	Self	r=-.191, p=.552	r=-.061, p=.850	r=.310, p=.327
	Parent	r=.305, p=.335	r=-.250, p=.433	r=.060, p=.853
RCADS: OCD	Self	r=-.073, p=.823	r=-.199, p=.34	r=.244, p=.483

Appendix 14: association between cognitive scores and sleepsuite performance				
	Parent	r=.043, p=.895	r=.021, p=.947	r=-.341, p=.279
RCADS: Depression	Self	r=.024, p=.941	r=-.072, p=.825	r=.115, p=.722
	Parent	r=.052, p=.872	r=.029, p=.928	r=-.040, p=.902
Conner's: Inattentive	Parent	r=.160, p=.620	r=-.029, p=.929	r=-.-210, p=.513
Conner's: Hyperactive impulsive	Parent	r=.086, p=.790	r=.124, p=.701	r=--.311, p=.326

*****=significant at p<.05

TS

Cognitive Domain (Measure)	*Animals (Number Correct)*	*Balloons Emotion (Commission Errors)*	*Balloons Gender (Commission Errors)*	*Mazes (Time To Target)*
Full Scale IQ (WASI 2 Subtest IQ)	r=.317, p=.291	r=.129, p=.676	r=.067, p=.867	r=-.008, p=.979
Working Memory: Verbal (WISC Digit Span)	r=-.040, p=.896	r=-.036, p=.908	r=-.191, p=.531	r=-.117, p=.702
Processing Speed (WISC Cancellation)	**r=-.639, p=.019***	r=-.021, p=.945	r=.241, p=.428	r=.329, p=.273
Inhibition (DKEFS Colour-Word Interference)	r=-.100, p=.746	r=-.452, p=.121	**r=-.626, p=.022***	r=.230, p=.449
Inhibition/Switching (DKEFS Colour-Word Interference)	r=-.016, p=.958	r=-.448, p=.125	r=-.402, p=.174	r=.436, p=.136
Verbal Memory: Short Delay (CVLT-C)	r=-.526, p=.065	r=-.323, p=.281	r=-.216, p=.478	r=.312, p=.300
Verbal Memory: Long Delay (CVLT-C)	r=-.331, p=.269	r=-.341, p=.254	r=-.190, p=.533	r=.271, p=.371
Working Memory: Motor (WMTB Block Recall)	r=.049, p=.874	r=-.145, p=.636	r=-.332, p=.268	r=-.338, p=.190
Motor Inhibition (Tea-Ch Walk, Don't Walk)	r=.154, p=.615	r=-.094, p=.761	r=-.304, p=.313	r=-.097, p=.752
Reaction Time (Grooved Pegboard, Dominant Hand)	r=.159, p=.603	r=-.434, p=.138	r=-.058, p=.852	r=.054, p=.862
Reaction Time (Grooved Pegboard, Non-Dominant Hand)	r=-.311, p=.300	r=.213, p=.485	r=.303, p=.314	**r=.597, p=.031***
Phonological Processing (CTOPP Blending Words)	r=.022, p=.945	r=.113, p=.726	r=.030, p=.926	r=-.276, p=.385

Control

Cognitive Measure	*Animals (Number Correct)*	*Balloons Emotion (Commission Errors)*	*Balloons Gender (Commission Errors)*	*Mazes (Time To Target)*
Full Scale IQ (WASI 2 Subtest IQ)	r=.215, p=.441	r=-.324, p=.304	r=-.146, p=.650	r=-.066, p=.822
Working Memory: Verbal (WISC Digit Span)	r=-.072, p=.799	r=.303, p=.339	r=-.190, p=.555	r=-.138, p=.637

Processing Speed (WISC Cancellation)	r=.199, p=.477	r=.032, p=.922	r=-.077, p=.812	r==.007, p=.980
Inhibition (DKEFS Colour-Word Interference)	r=.325, p=.237	r=-.325, p=.303	r=.124, p=.702	r=.058, p=.845
Inhibition/Switching (DKEFS Colour-Word Interference)	r=.278, p=.315	r=-.179, p=.577	r=.253, p=.427	r=-.013, p=.965
Verbal Memory: Short Delay (CVLT-C)	r=-.434, p=.121	r=.097, p=.764	r=-.054, p=.867	r=.108, p=.726
Verbal Memory: Long Delay (CVLT-C)	r=-.360, p=.206	r=.124, p=.700	r=-.091, p=.778	r=.136, p=.657
Working Memory: Motor (WMTB Block Recall)	r=-.282, p=.328	r=.471, p=.122	r=.105, p=.745	r=-.161, p=.599
Motor Inhibition (Tea-Ch Walk, Don't Walk)	r=.212, p=.449	r=.223, p=.485	r=-.478, p=.116	r=.220, r=.449
Reaction Time (Grooved Pegboard, Dominant Hand)	r=-.272, p=.348	r=.446, p=.146	r=-.130, p=.688	r=.151, p=.605
Reaction Time (Grooved Pegboard, Non-Dominant Hand)	r=-.176, p=.547	r=.296, r=.351	r=.197, p=.539	r=-.145, p=.622
Phonological Processing (CTOPP Blending Words)	r=.267, p=.378	r=-.375, p=.230	r=.022, p=.946	r=.043, p=.888